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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
OBSTETRICS AND GYNECOLOGY DEVICES PANEL

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Monday,  
July 22, 2002

Plaza Ballroom I and II  
DoubleTree Hotel  
1750 Rockville Pike  
Rockville, Maryland

FRIEDMAN & ASSOCIATES, COURT REPORTERS  
11923 Parklawn Drive, Suite 203  
Rockville, MD 20852  
(301) 881-8132

## IN ATTENDANCE:

Jorge D. Blanco, M.D., (Chair)  
Regional Perinatal Center  
Odessa Regional Hospital  
Odessa, TX

Carol L. Brown, M.D.  
Weill-Cornell Medical College  
Memorial Sloan-Kettering Cancer Center  
New York, NY

Anil K. Dubey, Ph.D., H.C.  
Department of Obstetrics and Gynecology  
George Washington University Medical Center  
Washington, D.C.

Kinley Larntz, Ph.D.  
School of Statistics  
University of Minnesota  
Scottsdale, AZ

Kleia R. Luckner, J.D., M.S.N.  
(Consumer Representative)  
Women's Ambulatory Health  
The Toledo Hospital  
Toledo, OH

Mary Lou Mooney, R.A.C.  
(Industry Representative)  
SenoRx, Inc.  
Aliso Viejo, CA

Kenneth L. Noller, M.D.  
Department of Obstetrics and Gynecology  
Tufts University Medical School  
Boston, MA

Mary Jo O'Sullivan, M.D.  
Department of Obstetrics and Gynecology  
University of Miami/Jackson Memorial Hospital, Hoetz Center  
Miami, FL

Subir Roy, M.D.  
Department of Obstetrics and Gynecology  
USC School of Medicine  
Los Angeles, CA

## IN ATTENDANCE:

David B. Seifer, M.D.  
Division of Reproductive Endocrinology and Infertility  
University of Medicine and Dentistry of New Jersey  
New Brunswick, NJ

Nancy C. Sharts-Hopko, Ph.D.  
College of Nursing  
Villanova University  
Villanova, PA

Gerald J. Shirk, M.D.  
OB/GYN Associates  
Cedar Rapids, IA

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1                                    P R O C E E D I N G S                                    (8:40 a.m.)

2                    DR. BLANCO: Good morning. I'd like to go  
3 ahead and call the 66th meeting of the Obstetrics and  
4 Gynecology Devices Panel to order this morning and would  
5 like to take care of a little business issues first, if we  
6 could. Just would like to remind everyone that there's  
7 sign-in sheets outside the door, if you would please sign  
8 in with your name and your affiliation, so that we have a  
9 record of everyone that was here.

10                    I always like to remind, and I'm reminded to  
11 remind the audience, that we don't really want any  
12 outbursts from the audience. Please, when it's the time  
13 for audience comments, we will recognize you. You can come  
14 to the mike to speak. At the time that you do, please make  
15 sure to state your name, any relationship that you may have  
16 with any company bringing business before this committee,  
17 any conflict of interest disclosure, including any travel  
18 per diem or any other relationship with the company.

19                    At this point, I'd like for the panel members  
20 to introduce themselves as we go around the table, if we'll  
21 go ahead and start on this side.

22                    MS. MOONEY: Mary Lou Mooney. I'm the vice  
23 president of clinical, regulatory, and quality for SenoRx.  
24 I'm the industry representative to the panel.

25                    MS. LUCKNER: Kleia Luckner, Toledo, Ohio. I'm

1 the clinical administrator for women's ambulatory, and I'm  
2 the consumer rep.

3 DR. NOLLER: Ken Noller, Boston, Massachusetts.  
4 I'm an obstetrician/gynecologist, panel member.

5 DR. DUBEY: Anil Dubey from George Washington  
6 University, embryologist, new to the panel.

7 DR. SEIFER: David Seifer, reproductive  
8 endocrinologist. I'm a panel member. New Brunswick, New  
9 Jersey.

10 DR. WHANG: I'm Joyce Whang. I'm the executive  
11 secretary of this panel.

12 DR. BLANCO: I'm Jorge, George, Blanco. I'm a  
13 perinatologist from Texas.

14 DR. BROWN: I'm Carol Brown. I'm a  
15 gynecological oncologist from New York City, New York.

16 DR. SHARTS-HOPKO: I'm Nancy Sharts-Hopko,  
17 professor in women's health, College of Nursing, Villanova  
18 University, near Philadelphia.

19 DR. O'SULLIVAN: Mary Jo O'Sullivan, University  
20 of Miami, panel member, OB/GYN.

21 DR. ROY: Subir Roy, reproductive  
22 endocrinologist, University of Southern California.

23 DR. LARNTZ: Kinley Larntz. I'm a professor  
24 emeritus of statistics, University of Minnesota, and I work  
25 as an independent statistical consultant.

1 DR. SHIRK: Dr. Gerry Shirk. I'm in clinical  
2 practice in Cedar Rapids, Iowa, and a clinical associate  
3 professor at the University of Iowa.

4 MS. BROGDON: I'm Nancy Brogdon. I'm the  
5 division director for the Division of Reproductive,  
6 Abdominal, and Radiological Devices, FDA.

7 DR. BLANCO: Thank you.

8 The next issue is introducing the FDA press  
9 contact, Sharon Snider. If you would please stand? Is she  
10 here?

11 MS. BROGDON: I don't believe she's here yet.

12 DR. BLANCO: Okay. Well, she will be here and  
13 she is your press contact.

14 All right. Let me go ahead and turn over the  
15 meeting to Dr. Whang for a few other items of housekeeping.

16 DR. WHANG: Good morning.

17 The next scheduled meeting of this Obstetrics  
18 and Gynecology Devices Panel is for October 21st and 22nd  
19 of this year.

20 Today, we have five temporary voting members,  
21 Dr. Anil Dubey, Dr. Kinley Larntz, Dr. Kenneth Noller, Dr.  
22 Subir Roy, and Dr. Gerald Shirk.

23 "Pursuant to the authority granted under the  
24 Medical Devices Advisory Committee Charter, dated October  
25 27th, 1990, and amended August 18th, 1999, I appoint the

1 following individuals as voting members of the Obstetrics  
2 and Gynecology Devices Panel for this meeting on July 22nd,  
3 2002: Anil K. Dubey, Ph.D., H.C., Kinley Larntz, Ph.D.,  
4 Kenneth L. Noller, M.D., Subir Roy, M.D., Gerald J. Shirk,  
5 M.D. For the record, these people are special government  
6 employees and are consultants to this panel. They have  
7 undergone the customary conflict of interest review and  
8 they have reviewed the material to be considered at this  
9 meeting," and this is signed by David W. Feigal, Jr., M.D.,  
10 M.P.H, the Director of the Center for Devices and  
11 Radiological Health.

12 I will now read the conflict of interest  
13 statement for this meeting. "The following announcement  
14 addresses conflict of interest issues associated with this  
15 meeting and is made a part of the record to preclude even  
16 the appearance of an impropriety.

17 "To determine if any conflict existed, the  
18 agency reviewed the submitted agenda and all financial  
19 interests reported by the committee participants. The  
20 conflict of interest statutes prohibit special government  
21 employees from participating in matters that could affect  
22 their or their employers' financial interests. However,  
23 the agency has determined that participation of certain  
24 members and consultants and the need for their services  
25 outweighs the potential conflict of interest involved and

1 is in the best interests of the government.

2 "Therefore, a waiver has been granted for Dr.  
3 Kinley Larntz for his interests in a firm that could  
4 potentially be affected by the panel's recommendations.  
5 The waiver allowing him to participate fully in today's  
6 deliberations involves his unrelated consulting services  
7 with the parent of a competing firm. He receives fees that  
8 range between \$10,001 and \$50,000 a year. Copies of this  
9 waiver may be obtained from the agency's Freedom of  
10 Information Office, Room 12A-15 of the Parklawn Building.

11 "In the event that the discussions involve any  
12 other products or firms not already on the agenda for which  
13 an FDA participant has a financial interest, the  
14 participant should excuse his or herself from such  
15 involvement and the exclusion will be noted for the record.

16 "With respect to all participants, we ask in  
17 the interest of fairness that all persons making statements  
18 or presentations disclose any current or previous financial  
19 involvement with any firm whose products they may wish to  
20 comment upon."

21 Today's transcripts are being taken by Friedman  
22 & Associates. They're in Rockville, Maryland, at (301)  
23 881-8132, and today's meeting is being videotaped by FDA  
24 Live. They're in Rockville, Maryland. They can be reached  
25 at (301) 984-0001.

1 Thank you.

2 DR. BLANCO: Thank you.

3 Moving right along, I'd like to introduce Mr.  
4 Colin Pollard, chief of the Obstetrics and Gynecology  
5 Devices Branch, who will make some introductory statements.

6 Colin?

7 MR. POLLARD: Thank you, Dr. Blanco.

8 I just have a couple of brief comments. So  
9 first of all, I just wanted to welcome all of you to our  
10 panel meeting today. I know several of you had to come  
11 from very far and all of you are taking time from very busy  
12 schedules to provide us with important input.

13 I, first of all, just wanted to announce that  
14 we have issued a Level 1 Guidance Document for Adhesion  
15 Barrier Devices. This is the culmination of a panel  
16 meeting that we had about two years ago. This guidance  
17 incorporates comments from the industry and clinical  
18 community and represents a joint collaboration with another  
19 division in our Office of Device Evaluation for these kinds  
20 of products, and we hope that it will further provide help  
21 to people developing products in this important area.

22 I'd like to next turn to the first agenda item.  
23 You may or may not remember that in May of 1998, FDA issued  
24 a Public Health Advisory on Vacuum-Assisted Deliveries and  
25 the devices used for them, essentially sharing information

1 that came out of our Mandatory Device Reporting System, and  
2 since that and, of course, that advisory itself generated a  
3 lot of interest and activity and comments and concerns  
4 about these kinds of devices, and since that point, our  
5 Office of Surveillance and Biometrics has done continued  
6 work in that area and the Office of Surveillance and  
7 Biometrics has taken the initiative to apprise the panel  
8 and apprise us, of course, on the results from that, and  
9 this represents an effort on their part to engage with all  
10 of the different advisory panels to show and to illustrate  
11 some of the things the agency is doing in the area of  
12 postmarket following various devices.

13 This is essentially an informational  
14 presentation just to let you know what's going on. I think  
15 certainly at Dr. Blanco's discretion, he'll entertain a few  
16 questions, but essentially it's just to let you know what's  
17 going on in this area. So with that, I'd like to introduce  
18 Danica Marinac-Dabic, who will begin the presentation.

19 Thank you.

20 DR. BLANCO: All right. Thank you, Colin.

21 While we're waiting for Dr. Dabic, just wanted  
22 to remind everyone that we will try to keep on time. So  
23 make sure all the speakers that are coming, that you do  
24 stay on time. We'd like to be on time.

25 Welcome.

1 DR. MARINAC-DABIC: Good morning.

2 My name is Danica Marinac-Dabic. I work for  
3 the Epidemiology Branch of the Office of Surveillance and  
4 Biometrics here at CDRH. Dr. Barry Schiffrin and I would  
5 like to thank you for the opportunity to be able to present  
6 this morning an update on the CDRH postmarket activities in  
7 the area of vacuum-assisted delivery devices.

8 As an introduction to Dr. Schiffrin's talk, I  
9 would like first to give you a brief background information  
10 on the events leading to the 1998 Public Health Advisory as  
11 well as an update on the number of the reports received by  
12 the agency in the years following the advisory. After  
13 that, as the main part of today's presentation, Dr.  
14 Schiffrin as the principal investigator will give you  
15 results of the Phase 1 of the FDA-sponsored study titled  
16 "Adverse Outcomes Associated With Vacuum-Assisted  
17 Deliveries."

18 The number of reports received by the FDA  
19 related to vacuum-assisted delivery devices began to  
20 increase in years 1993 and 1994. As you can see prior to  
21 that, on average, we received one report per year. The  
22 total number of reports that the Public Health Advisory was  
23 based on is 30, and as you can see, the distribution, the  
24 year distribution was presented in this slide. This is  
25 essentially the same number of reports, the same time

1 period, the same database. It just presents a distribution  
2 of events and serious injuries and you can see there,  
3 particularly in the period from 1994 to 1997, we see the  
4 increased number of death reports associated with vacuum.

5 Major types of complications reported to us  
6 were subgaleal hemorrhage, cephalhematoma, and intracranial  
7 hemorrhage. The information that we were able to obtain  
8 from those adverse event reports were very limited. In  
9 addition to the number of deaths and injuries that were  
10 reported and also the types of complications, we were able  
11 to see that all major vacuum-assisted delivery devices  
12 manufacturers were represented as well as all vacuum types.  
13 However, the most critical information was sometimes  
14 missing from those reports and particularly the patterns of  
15 use of vacuum, including number of events or duration of  
16 vacuum application. Also, the clinical environment data  
17 were missing, including the fetal and maternal condition  
18 and timing of injuries.

19 I think it's important to put the data that we  
20 have received into the perspective, and I would like to  
21 just give this table to you as a national data that we were  
22 able to obtain prior to the Public Health Advisory that was  
23 published in 1997, the National Vital Statistics Report,  
24 reflecting the data from the 1995 and we can see that at  
25 that year, 5.9 percent of total deliveries occurred with

1 the assistance of the vacuum. One can also notice a  
2 dramatic increase in the use of vacuum from year 1989 when  
3 only 3.5 percent of all deliveries was completed with the  
4 assistance of the vacuum extraction.

5 Of course, there were numerous possible reasons  
6 for increased number of reports and some of them are listed  
7 on this slide. First one that I'd like to point out is  
8 increasing vacuum use, as documented by the national data,  
9 also the second possible reason would be the change in the  
10 reporting requirement, namely the introduction of the User  
11 Facility Reports that overlapped with the year when we  
12 began to notice an increased number of the reports. Also  
13 potential underreporting in previous years was also  
14 possible reason as well as the increased incidence rate of  
15 adverse events.

16 CDRH convened an ad hoc committee of experts to  
17 look into this issue and provide recommendation. On this  
18 slide, we have listed some of the activities that the  
19 committee undertook, including the adverse events reports  
20 review, followed by the extensive literature and labeling  
21 review, dialogue with manufacturers, and also dialogue with  
22 clinical users. We performed three user facility  
23 investigations at that time and consulted with professional  
24 organizations, including ACOG, American College of Nurse-  
25 Midwives, American Academy of Pediatrics, and finally,

1 after internal and external review, the Public Health  
2 Advisory was issued on May 21st, 1998, and it was titled  
3 "Need for CAUTION When Using Vacuum-Assisted Delivery  
4 Devices."

5 The purpose of the Public Health Advisory was  
6 to advise medical community that vacuum may cause serious  
7 or fatal complications and also to provide guidance on how  
8 to minimize the risk. It provided detailed  
9 recommendations. They were meant for both obstetrical and  
10 neonatal community and stated here that only trained  
11 professionals should be using the vacuum, also to be aware  
12 of indications, contraindications and precautions, always  
13 read the instructions, and, what's very important, to alarm  
14 the neonatal care community that device was used so they  
15 can look for the specific signs and symptoms for  
16 complications, of complications, and of course report this  
17 to the FDA, and these are some of the post-advisory  
18 activities ongoing here at the Center of Devices and  
19 Radiological Health. Of course, the review of the adverse  
20 event reports continues and as Colin Pollard just said, the  
21 FDA also sponsored the study titled "Adverse Outcomes  
22 Associated with Vacuum-Assisted Delivery Devices."

23 This is just a brief update on the number of  
24 reports that we have received. As you can see in the year  
25 following the Public Health Advisory, 1998, there was a

1 peak of the reports and then the number declines. The last  
2 data that we have ended with the end of month of June this  
3 year. All together, we have received 170 reports, 26 of  
4 them were deaths and 144 of serious injuries. Nationally,  
5 we can see the increase of the vacuum continues. The  
6 number for the 1998 is 6 percent of total deliveries.

7 With this, I'd like to turn the podium over to  
8 Dr. Schifrin, who will present the Phase 1 of our joint  
9 study. He was the principal investigator for this. The  
10 analysis of the second phase is underway. So you'll be  
11 able to see only the results of the first phase today.

12 Thank you very much.

13 DR. BLANCO: Thank you very much.

14 DR. SCHIFRIN: My name is Barry Schifrin. I'm  
15 an obstetrician perinatologist. I'm professor of  
16 obstetrics and gynecology at Loma Linda, and I'm director  
17 of the Residency Program at Glendale Adventist Medical  
18 Center in Glendale, California, and I want to thank the FDA  
19 for the opportunity to begin and undertake this study and  
20 it was as informative and to me provided great revelations,  
21 notwithstanding the fact that I had thought I had some  
22 familiarity with the subject.

23 DR. BLANCO: Excuse me, Dr. Schifrin.

24 Just for the record, any conflict of interest?

25 DR. SCHIFRIN: No, no. No conflict.

1 DR. BLANCO: Sorry. Thank you.

2 DR. SCHIFRIN: No conflict.

3 The primary focus of the study was to look at  
4 the other apparatus and not only the vacuum apparatus  
5 itself but essentially the decisionmaking apparatus  
6 surrounding the use of the vacuum device, and for this  
7 purpose, as suggested by Danica Marinac, we needed to know  
8 something about the condition of the baby, the setting, the  
9 circumstances of labor, and the number of factors about the  
10 previous history, about the physical attributes and  
11 presentation of the fetus to be able to make sense out of  
12 the use patterns of the vacuum.

13 The other issue and perhaps drawback of the  
14 advisory was the implicit notion that all of the adverse  
15 outcomes associated with vacuum deliveries were in fact  
16 related to the vacuum itself, and the fact is that a number  
17 of the babies who had ischemic injuries, it is obvious that  
18 those could occur at any time. We could understand that  
19 traumatic injuries related to adverse outcome might  
20 certainly be related to the delivery and this seemingly  
21 characteristic hemorrhagic phenomenon called the subgaleal  
22 was almost certainly related to the vacuum itself, and  
23 while it is reasonable, also, to attribute intracranial  
24 hemorrhage to the vacuum and forceps, the fact is, as  
25 you'll see, the most frequent kind of neurologic injury

1 associated with the vacuum is hypoxic-ischemic  
2 encephalopathy and not the subgaleal hemorrhage, the  
3 intracranial hemorrhage, or even the traumatic hemorrhage.

4 The cases, and there were 203, and they derived  
5 from malpractice cases, peer-review, referrals. They come  
6 from many sources, hospital sizes, and they clearly  
7 represent the group of patients at increased risk of  
8 adverse outcome. They were attended in the vast majority  
9 of them by board-certified obstetricians and a small group  
10 by obstetrical residents, midwives and others who are  
11 multiple providers.

12 The important emphasis here is that these  
13 patients were not selected. They were selected clearly  
14 because they had a vacuum, but it was not the vacuum  
15 necessarily that brought the patient to attention, and we  
16 studied these 203 patients, looking at numerous obstetrical  
17 and neonatal factors related not only to the delivery  
18 itself but those factors related to the process, to the  
19 decisionmaking apparatus, and, as we'll see just briefly,  
20 in terms of physician behavior.

21 I will share with you, now that you have copies  
22 of all of these data in the handout, the majority of the  
23 patients were nulligravida, nulliparita. They had no  
24 previous vaginal delivery and almost half of them were  
25 high-risk by one of the rather loose definition. You can

1 see the incidence of the various other problems which would  
2 confer risk on the patient population.

3 You can see that as part of the actual delivery  
4 itself, that forceps were used in 8 percent, vacuum -- I'm  
5 sorry -- forceps, more than one application of forceps,  
6 more than -- that should be two applications of the vacuum  
7 were applied in 50 percent of them. That is a rather high  
8 number. There were 4 percent of the patients had ruptured  
9 uterus and almost 25 percent of the patients was a shoulder  
10 dystocia encountered, an extraordinary incidence. A normal  
11 expected incidence of shoulder dystocia associated with  
12 vacuum might be anywhere from 5 to 10 percent.

13 The features of labor that the majority of  
14 patients were in fact in spontaneous labor, but a  
15 considerable percentage were in fact induced. More than  
16 half had epidural anesthesia and almost 40 percent of them  
17 had a prolonged second stage of labor. The indications by  
18 parity, this is para zero, are those who had no previous  
19 vaginal delivery, para 1, those who had previous delivery  
20 whether vaginal or not, and then there's all cases, and I  
21 emphasize to you that these numbers add up to more than 100  
22 percent because very many of them, there were multiple  
23 "indications" for use of the procedure.

24 We believe it is a test of the quality of  
25 obstetrical care that the number of emergency panic

1 deliveries that are required is in fact a test of the  
2 quality of obstetrical care that is being delivered. The  
3 Hail Mary pass may be good theater but it is not good  
4 football. Emergency deliveries may certainly be necessary  
5 but it's hard to relate it to good obstetrics.

6           One of the features and rather curious features  
7 is that one gets the notion that many of these deliveries,  
8 they are trying to facilitate or speed up the delivery, and  
9 under normal circumstances having the patient begin pushing  
10 before she is fully dilated, before the cervix is fully out  
11 of the way, is probably not a very productive practice.  
12 Fundal pressure. This applies to the use of manual  
13 pressure on the uterus to help to get the baby stationed.  
14 This is not in response to the shoulder dystocia but this  
15 simply an attempt to help with the vacuum delivery, and the  
16 number and frequency of these maneuvers speaks for attempts  
17 at intervention.

18           These two slides in your handout are the same.  
19 They just present one as tabular, one as graphic, and what  
20 you see here is the route, the ultimate route of delivery.  
21 It is necessary to remember that all of these patients had  
22 vacuum as almost invariably the first attempt to get the  
23 baby delivered, and you can see that, depending upon which  
24 group, in all cases, only about 60 percent at max of the  
25 patients were actually delivered by the vacuum. I share

1 with you that a normal failure rate is about 5 percent.  
2 That is 5, perhaps 6 to 7, percent, and the conventional  
3 literature suggest that. In this case, it was at least 40  
4 percent or more, depending upon the group.

5 In terms of the neonatal outcome, you can see  
6 that the majority of the babies had low Apgars, certainly  
7 at one minute, a third of them had low Apgars at five  
8 minutes, 25 percent or thereabouts were large, greater than  
9 4,000, more than almost two-thirds of the babies required  
10 admission to the neonatal intensive care unit, and maybe 4  
11 percent or thereabouts required extensive resuscitation.

12 In terms of the neonatal complications, they're  
13 listed for you here. The item of interest with regard to  
14 the vacuum was the appearance of more than half had  
15 cephalhematoma and more than half required a neonatal  
16 length of stay more than two days.

17 In terms of the radiologic findings, you can  
18 see that about 15 percent of the population had subgaleal  
19 hemorrhage but that the most frequent injury in this group  
20 was the injury associated with ischemic brain injury.  
21 About a little more than a quarter had bleed with or  
22 without some of these co-existed, of course, but far and  
23 away, the most common cause of the injury was ischemic and  
24 not obviously traumatic or hemorrhagic.

25 In terms of the long-term outcome, there was

1 three stillbirths. There were 10 neonatal deaths, two  
2 later deaths. There were 12 fractures, 20 permanent Erb's  
3 palsy, which represented about 40 percent of the babies who  
4 had shoulder dystocia, and 126 or 62 percent of the babies  
5 had cerebral palsy, in great measure explained by the  
6 providence of the cases, and this illustrates when the  
7 timing, going to use the fetal monitor in an attempt to  
8 time the ischemic event, and you can see that the vast  
9 majority or not the vast majority but certainly about half  
10 of the patients are in fact injured. The babies are  
11 injured during the second stage prior to the application of  
12 the vacuum.

13 I share with you this tracing, and for those of  
14 you not familiar with the tracing, I will try simply to  
15 deal with the major points that I'm trying to emphasize in  
16 this case, and it will illustrate very briefly how we use  
17 the monitor, the fetal monitor, to make the diagnosis of  
18 injury.

19 If you focus only on the red, you can see that  
20 the mother is having frequent contractions. Those  
21 contractions are about a minute and a half apart. So I  
22 think it's about 15 minutes across that slide, and the red  
23 arrow represents pushing with contractions, and you can see  
24 with each effort of pushing, there is a deceleration in the  
25 heart rate. The horizontal red line is the baby's baseline

1     which it has had for its entire labor and the first two  
2     hours of the second stage in this labor, and I call your  
3     attention now to the green arrow which is what has happened  
4     to the baseline as the baby develops greater and greater  
5     stress, the decelerations become longer. There are periods  
6     of time just before the red vertical arrow where there is  
7     no baseline between the contractions. The baby is  
8     obviously deteriorating under these circumstances and  
9     notice that the relentless pushing is maintained despite  
10    the deterioration of the fetal condition.

11                 Here, you see on the left the two arrows  
12    associated with pushing and now for the next four  
13    contractions there are no decelerations and you have a high  
14    flat heart rate pattern with no variability. I believe  
15    that is the diagnosis of neurologic injury. At the end of  
16    this slide, at the right edge of this slide, they apply a  
17    vacuum which creates the beginning of that bradycardia.  
18    They take the vacuum off and apply the forceps. They take  
19    the forceps off and apply the vacuum. They take the vacuum  
20    off, apply the forceps. They discontinue the forceps. The  
21    baby's in the middle of this profound bradycardia. The  
22    head is stuck. There is shoulder dystocia. They try  
23    various maneuvers to get the baby delivered. The baby will  
24    eventually have severe neurologic injury, including  
25    subgaleal hemorrhage and Erb's palsy. What we believe that

1     this approach allows you to do is to show that  
2     notwithstanding the other problems, the baby's initial at  
3     least neurologic injury occurred long before, reasonably  
4     before the application of the vacuum.

5             The hypotheses for Phase II relate, as might be  
6     inferred, that experience was not protective of injury and,  
7     parenthetically, the largest number of vacuum applications  
8     in this study was 16. The longest duration of application  
9     was the better part of an hour. These are seemingly out of  
10    the realm of what experience teaches us, that as I  
11    suggested before, that the urgency of delivery is not an  
12    unreasonable endpoint for evaluating the quality of  
13    obstetrical care. The methodology we will use, as I say,  
14    is a control group and we have derived a control group of  
15    almost 200 patients from four California hospitals  
16    involving both private community hospitals, university  
17    hospitals, and a large municipal hospital which is  
18    university-affiliated.

19            The objective is to understand not only the  
20    effects of the vacuum itself but the conduct of the labor  
21    in the second stage and to try to answer or help to answer  
22    the notion of how these injuries occur and with the  
23    understanding that it is unlikely to be just a simple  
24    problem with the vacuum.

25            Thank you very much.

1 DR. BLANCO: Thank you, Dr. Schifrin.

2 Does any of the panel members have any  
3 questions or comments concerning the presentation?

4 DR. O'SULLIVAN: Barry, considering that this  
5 is only the cases that were reported, in the process of  
6 looking, did you have the opportunity in the control  
7 hospitals or in the control cases to look at just vacuums  
8 in general?

9 DR. SCHIFRIN: Yes, that is what we did. The  
10 way you got into the control group is you had a vacuum  
11 delivery.

12 DR. O'SULLIVAN: Okay, and the incidence of  
13 complications associated with those?

14 DR. SCHIFRIN: That will be the subject, but it  
15 is quite small, and the most obvious is that the failure  
16 rate in the controls is 5 percent, 6 percent, something  
17 like that, and the shoulder --

18 DR. O'SULLIVAN: I'm sorry. I guess I was not  
19 quite listening at that point.

20 DR. SCHIFRIN: The shoulder dystocia rate was  
21 about 5 percent in those. So simply the most stunning  
22 statistic was the failure rate of about 50 percent of the  
23 vacuum. This is everybody. A vacuum is tried and it in  
24 fact failed 50 percent.

25 Just as a sidelight, there was no simultaneous

1 preparation for Caesarean section where it was failed. So  
2 this creates a scenario where you have to keep doing it.  
3 You have to keep proceeding because having not anticipated  
4 failure, you're obliged now to make the best you can under  
5 the circumstances.

6 DR. LARNTZ: This is Kinley Larntz.

7 I'm a newcomer to this panel and just a  
8 statistician, but I would have thought the control group,  
9 if you're worried about the vacuum, the effect of the  
10 vacuum, you'd have a control group that would be not  
11 vacuum-assisted.

12 DR. SCHIFRIN: I'm sorry?

13 DR. LARNTZ: You would have a control group  
14 that would be not vacuum-assisted, and I think that would  
15 be important to compare if you were interested in the  
16 effect of the vacuum.

17 DR. SCHIFRIN: We would very much have loved  
18 your input at the time we did this. We made a number of  
19 efforts to try to satisfy that issue and could not come up  
20 with a reasonable strategy to do that since the  
21 decisionmaking apparatus does not make that, it seems to  
22 me, as satisfying a comparison as you might think.

23 We certainly went through it and this went  
24 through a large number of debates about the control group.  
25 The only thing I can say is I'd be happy -- there's perhaps

1 not enough time to share all of the issues with you.

2 DR. NOLLER: Because now an attending must be  
3 present when a resident does deliveries, is it going to be  
4 possible in Phase II for you to determine who actually  
5 applied the device and whether it was applied multiple  
6 times, who did it each time?

7 DR. SCHIFRIN: I share with you two pieces of  
8 information. Medical records are hopelessly inadequate for  
9 obtaining that and that may be one of the ultimate  
10 recommendations that will come out of this. The second  
11 issue -- and I would challenge you all who are clinically  
12 involved. There is an ICD-9 code. I do not remember what  
13 it is offhand. There is an ICD-9 code for a failed vacuum.  
14 In no hospital that we have yet called, and we've called a  
15 number of them, including all the hospitals that have  
16 participated in the study, no one has any record of a coded  
17 failed forceps. You can't find it in the record.

18 The last thing I would share with you is the  
19 deposition statement of one of the physicians who was  
20 peripherally involved in one of those cases, and he said  
21 simply "if it was an easy vacuum, I might not even record  
22 it in the delivery note." So this approach makes this  
23 undertaking, trying to make sense out of the medical  
24 records, challenging to say the least.

25 DR. NOLLER: That was really my point. I don't

1 think you're going to be able to tell the difference  
2 between attending and resident deliveries. It'll all be in  
3 one big bundle probably.

4 DR. SCHIFRIN: The interesting thing, at least,  
5 about the control group, about the study group, is that the  
6 vast majority of them are board-certified obstetricians  
7 without a resident anywhere in sight.

8 DR. BLANCO: Any other comment and questions?  
9 I just wanted to ask you. One of the things that came  
10 across in your presentation to me is the fact that the  
11 indications obviously are going to be very important, and  
12 one of the things that a lot of clinicians utilize the  
13 vacuum as sort of what you said, the emergent patient who's  
14 not quite ready to, you know, be delivered any other way  
15 and so you "use the vacuum."

16 I wonder. Are you going to be able to separate  
17 from your data in that setting whether it was bad judgment  
18 in applying that as opposed to, you know, the vacuum itself  
19 creating the problem? Do you understand where I'm getting  
20 at?

21 DR. SCHIFRIN: I understand, and I'm going to  
22 try to answer charily. I think this is about behavior. I  
23 don't know how you explain 16 applications of a vacuum  
24 under any clinical circumstances. There are portions of  
25 these data that are difficult emotionally to deal with,

1     that somebody would apply a vacuum 16 times or leave it on  
2     for an hour.

3                 You may have seen the "20/20" show and this is  
4     just hard to deal with, but ultimately it seems to me that,  
5     as I suggested in the presentation, that we need to  
6     decrease the urgency of the deliveries and maybe that is a  
7     test of what we can do, and as I tried to share with you,  
8     with the tracing itself, that the conduct of the second  
9     stage, that the maintenance of the pushing as the baby is  
10    deteriorating is something we need to perhaps rethink and  
11    that the whole objective is to make it an easy vaginal  
12    delivery or easy Caesarean section. There's nothing in  
13    this study thus far that suggests we should do away with  
14    vacuums.

15                DR. BLANCO: Thank you very much. Thank you,  
16    both of you, for a very nice presentation of the  
17    information to the panel.

18                I would like to go ahead and continue with the  
19    rest of the panel meeting, and before we begin, and we'll  
20    begin with the open public hearing, I'd like to go ahead  
21    and remind all of the presenters to introduce themselves  
22    and to describe any potential conflict of interest. I also  
23    would like to remind the presenters, to the panel who have  
24    not already done so, that they should provide the FDA with  
25    a hard copy of their remarks, including overheads. Kathy

1 Daws-Kopp -- Kathy, would you please stand? -- will be  
2 available at the podium when you come up to collect these  
3 from you at that time.

4 Having said that, we'll go ahead and begin with  
5 the folks who have signed in and requested time for  
6 comments to the panel during the open public hearing. I  
7 just would like to remind the speakers that we normally  
8 have about five minutes for each of your presentations, and  
9 then at the end of the speakers that we know would like to  
10 present before the panel, we'll open it up if there's  
11 anyone else in the audience who would like to make some  
12 brief comments.

13 The first person that I have on my list is Ms.  
14 Gabriella Avina, R.N., from Martinez, California, if you  
15 would please come forward.

16 Thank you.

17 MS. AVINA: Thank you. Good morning. Please  
18 keep in mind that it's 6:20 in California, and I just got  
19 here last night. But thank you very much. My name is  
20 Gabriella Avina, and I appreciate the chance to share my  
21 story today.

22 I'd first like to share with you this picture,  
23 I know you can't see it, but it's of my family, and as you  
24 can see, that picture's very full. So we were done with  
25 our family planning. I'd like to --

1 DR. BLANCO: I'm sorry. Would you please, if  
2 you have any affiliation with an organization --

3 MS. AVINA: I was just getting to that.

4 DR. BLANCO: Thank you.

5 MS. AVINA: My trip today was paid for by  
6 Conceptus. I'm being reimbursed for my expenses, and my  
7 husband and I did purchase shortly after having the device  
8 implanted, we did purchase a small amount of stock.

9 Is that all you needed to know?

10 DR. BLANCO: Thank you. That's fine.

11 MS. AVINA: I am a registered nurse and I have  
12 been a nurse for 16 years. That time has been spent in the  
13 maternal/child field of nursing, and in 1991, I received a  
14 Master's degree with an emphasis on reproductive health.  
15 I'm married. I have three children, and after the birth of  
16 my second child, we had made the decision to not have any  
17 more children.

18 I researched my options very carefully and at  
19 that time made the decision that I didn't want to have  
20 surgery because I'd already had several surgeries for  
21 endometriosis and then I had to have an emergency colectomy  
22 after my second daughter. So we opted to forego for the  
23 most important reason, that I was just too busy to have  
24 surgery and go through the operation and the recovery. So  
25 in October of '98, I had an IUD placed. Seven months

1 later, I found out I was pregnant with my third son, my  
2 third child, and it was a very complicated pregnancy but he  
3 was born in a healthy delivery in January. So we were  
4 faced with the same decision again, what to do about birth  
5 control.

6 So after some discussion, actually lots of  
7 discussion, I convinced my husband to have a vasectomy, and  
8 in March of 2000, he had -- I'm going to spare you his  
9 story about his vasectomy because that would ruin the day  
10 for most. He had his sperm analysis in May, and it was  
11 virtually clear. It was negative for sperm, but on the  
12 advice of our physician, he was to return in 60 to 90 days  
13 and have a repeated sperm analysis. So he returned and had  
14 a sperm count of 70 million, which was so high that they  
15 assured us that was a lab error and being in the medical  
16 field, I was sure it was a lab error.

17 So I calmed him by telling him, we'll just do  
18 another analysis in the morning and it'll be fine, and he  
19 did, he repeated it again without abstinence. It was 36  
20 million, and he was devastated and all I could think about  
21 was what are we going to do now? So I was hoping there was  
22 still some small possibility that that wasn't correct. So  
23 being that I'm employed in a reproductive health center, I  
24 took some sperm with me to work and had our embryologist  
25 look at it and she assured me that those tests were in fact

1 correct.

2 So it was about that time that I heard about  
3 the clinical trials for Essure and it didn't take too much  
4 time for me to decide that I had nothing to lose, really.  
5 So in October of 2000, I had the device implanted, and in  
6 January of 2001, I had my hysterosalpingogram, which  
7 documented that I was blocked. It brought about a peace to  
8 my life and to my relationship that I cannot express to  
9 you. To have the history that we had with having children,  
10 we needed to find something that we could go about our life  
11 and our marriage with comfort and security. That's what  
12 the Essure device did for us.

13 In closing, I'd like to say one last thing. In  
14 the beginning, I told you that I'm a wife and I'm a mommy  
15 and I'm a nurse, but most importantly, I am a woman, and I  
16 speak for all women today when I ask for you to allow us to  
17 have another contraceptive option because we deserve it.

18 Thank you very much.

19 DR. BLANCO: Thank you.

20 Our next speaker that I have on the list is  
21 Caroline Costello from the Division of Reproductive Health,  
22 Centers for Disease Control.

23 MS. COSTELLO: Good morning. My name is  
24 Caroline Costello, and I work in the Division of  
25 Reproductive Health at the Centers for Disease Control.

1 I will be here representing the CREST Study  
2 Team and my colleagues at CDC and Bert Peterson at the WHO.  
3 I was invited here today to discuss the sterilization  
4 failure method, sterilization failure rates documented in  
5 the largest perspective U.S. study on female tubal  
6 sterilization. The U.S. Collaborative Review of  
7 Sterilization is often referred to by the acronym CREST and  
8 was conducted by the CDC and with support from the National  
9 Institutes of Child Health and Human Development.

10 Between 1978 and 1987, the CREST Study enrolled  
11 women scheduled for tubal sterilization at one of 15  
12 participating medical centers in nine U.S. cities. A total  
13 of 12,138 women were enrolled. Follow-up was attempted  
14 annually by telephone for five years. Women who enrolled  
15 before 1983 or earlier also received an additional follow-  
16 up interview eight to 14 years after the sterilization. A  
17 woman's follow-up ceased only if she refused to be  
18 interviewed, had died or had aborted a pregnancy, repeat  
19 tubal sterilization, sterilization reversal or  
20 hysterectomy.

21 For the analysis of pregnancy following tubal  
22 sterilization, the CREST data set was restricted to women  
23 who had the same method of tubal sterilization on each  
24 fallopian tube and whose method of tubal occlusion was  
25 laparoscopic unipolar coagulation, bipolar coagulation,

1     silicone rubber band application, or spring clip  
2     application or partial salpingectomy performed by  
3     laparotomy. The final analysis data set included 10,685  
4     women whose median age at the time of sterilization was 30.  
5     Most women were white non-Hispanic or black non-Hispanic  
6     and almost 80 percent had a high school degree. Eighty-two  
7     percent were currently married or had previously been  
8     married and almost 90 percent had been pregnant at least  
9     twice.

10                 Of this CREST subset, approximately 90 percent  
11     of the women were interviewed at the first year of follow-  
12     up, 75 percent of women were interviewed at the fifth year  
13     of follow-up, and 60 percent had the extended follow-up  
14     eight to 14 years after sterilization. During the annual  
15     telephone follow-up interview, women were asked, since your  
16     tubal sterilization, have you had a positive pregnancy test  
17     or been told by a physician that you were pregnant? If a  
18     woman responded affirmatively, the interviewer then  
19     completed a separate form which requested detailed  
20     information on the pregnancy. The information requested  
21     was the date of last menstrual period, date of pregnancy  
22     diagnosis and gestational age at diagnosis, date pregnancy  
23     ended and the gestational age at termination. Whenever  
24     possible, medical records were obtained for review.  
25     Requested records included results of pregnancy test,

1     ultrasound exams, et cetera.

2             All information collected on each pregnancy  
3     that was reported during the CREST follow-up was thoroughly  
4     evaluated by the CDC principal investigator, Bud Peterson,  
5     and the project director at the medical site where the  
6     sterilization was performed. The pregnancies were  
7     classified into four groups: true sterilization failures,  
8     luteal phase pregnancies, which refers to pregnancies  
9     conceived prior to sterilization but identified after the  
10    procedure, pregnancies that occurred after reanastomosis or  
11    in vitro fertilization, and pregnancies with too little  
12    information to be classified into the previous three  
13    categories. A total of 143 of the pregnancies were  
14    classified as true sterilization failures, 34 were  
15    classified as luteal phase pregnancies, and 16 pregnancies  
16    occurred after tubal reanastomosis or in vitro  
17    fertilization. Five pregnancies remained unclassified  
18    because of insufficient information.

19            The life table statistical method was used to  
20    calculate the cumulative probability of pregnancy per  
21    thousand sterilizations at each year following the  
22    procedure. The cumulative probability with 95 percent  
23    confidence intervals are plotted in this figure. At one-  
24    year post sterilization, the probability of having a  
25    pregnancy following sterilization was 5.5 per 1,000

1 procedures. The 95 percent confidence was 4.1 to 6.9 per  
2 1,000. At each additional year since sterilization, the  
3 cumulative probability of pregnancy increased. By five  
4 years since sterilization, the cumulative probability of  
5 pregnancy was 13.1 per 1,000 sterilizations, and by 10  
6 years, the cumulative probability was 18.5 pregnancies per  
7 1,000 sterilizations or approaching 2 percent. This plot  
8 demonstrates the continuing risk for sterilization failure,  
9 even after several years following the procedure.

10 The cumulative probabilities of pregnancy per  
11 1,000 procedures are plotted in this figure. The  
12 difference in cumulative probabilities by method of  
13 sterilization indicates the substantial difference in the  
14 sterilization effectiveness by methods. The most effective  
15 methods at preventing pregnancy were unipolar coagulation  
16 and postpartum partial salpingectomy, each with a 10-year  
17 cumulative probability of 7.5 pregnancies per 1,000  
18 procedures. The method with the highest cumulative  
19 probability of failure was laparoscopic spring clip  
20 application with a 10-year cumulative probability of 36.5  
21 pregnancies per 1,000 procedures or 3.6 percent.

22 The cumulative probability of pregnancy by age  
23 of sterilization is plotted here in this figure. The  
24 cumulative probability is the demonstrated difference in  
25 the risk of pregnancy by age of sterilization. Women who

1 were younger at sterilization were more likely than women  
2 older at sterilization to experience the sterilization  
3 failure. The difference in cumulative probability of  
4 pregnancy by age group grew more pronounced as the time  
5 since sterilization grew. The 10-year cumulative  
6 probability of pregnancy for women aged 18 to 27 was  
7 approximately 33 per 1,000 sterilizations while women who  
8 were at 34 to 44 years of age had a 10-year cumulative  
9 probability of approximately 6 percent, 6 per 1,000  
10 sterilizations.

11 Several factors were analyzed in multivariate  
12 analysis for their impact on the relative risk of  
13 sterilization failure. Only sterilization method, age at  
14 sterilization, race/ethnicity and study site were  
15 significant predictors of pregnancy following tubal  
16 sterilization in the multivariate analysis. After  
17 adjustment for other factors in the model, interval partial  
18 salpingectomy, spring clip application and bipolar  
19 coagulation were significantly more likely than postpartum  
20 partial salpingectomy to result in sterilization failure.  
21 After adjustment for other factors in the model as an age  
22 group, women younger than 34 at sterilization have  
23 pregnancy risks that are at least two times greater than  
24 the risk of pregnancy for the group of women 34 and older  
25 at sterilization. Black non-Hispanic women were also at

1 significantly greater risk for sterilization failure than  
2 were the white non-Hispanic women.

3 Of the 143 pregnancies that were true  
4 sterilization failures, almost 33 percent were ectopic  
5 pregnancies, 46 of these pregnancies occurred within the  
6 fallopian tube, the other ectopic was an invariate  
7 pregnancy. The proportion of pregnancies or ectopic varied  
8 substantially by sterilization method. Of the pregnancies  
9 following bipolar sterilization, 65 percent were ectopic  
10 compared to 15 percent of pregnancies following spring clip  
11 application. The cumulative probability and 95 percent  
12 confidence interval for ectopic pregnancy per 1,000  
13 sterilization procedures is plotted here for 1, 5 and 10  
14 years following sterilization. At one-year post-  
15 sterilization, the cumulative probability for ectopic  
16 pregnancy was .7 per 1,000 procedures with a 95 percent  
17 confidence interval of .2 to 1.2 per 1,000 procedures. Of  
18 the time since sterilization, the cumulative probability of  
19 an ectopic pregnancy increased. By five years, the  
20 cumulative probability of ectopic pregnancy was 4.0 per  
21 1,000 procedures and by 10 years, it was 7.3 per 1,000  
22 procedures. The plot demonstrates the continuing risk of  
23 ectopic pregnancy, even several years following the  
24 procedure.

25 The annual rate of ectopic pregnancy in the

1 fourth through 10 years after sterilization was no lower  
2 than the annual rate of ectopic pregnancy in the first  
3 three years. For the fourth through the 10th years, the  
4 rate was .8 ectopic pregnancies per 1,000 procedures  
5 annually compared to the annual rate of .7 per 1,000  
6 procedures in the first three years.

7 Similar factors that influence risk of all  
8 types of pregnancies, such as sterilization method, age at  
9 sterilization and race/ethnicity, were predictors of  
10 ectopic pregnancy following sterilization, with the  
11 exception of the additional predictability of having a  
12 history of pelvic inflammatory disease.

13 From the large CREST Study, it is evident tubal  
14 sterilization is a highly effective method of preventing  
15 pregnancy. However, pregnancies can occur. Because the  
16 CREST prolonged study follow-up, the rate of pregnancies  
17 following sterilization was substantially higher than rates  
18 generally reported. The prolonged follow-up also  
19 demonstrated that pregnancies can continue to occur at  
20 greater than one to two years after sterilization. Among  
21 women who had pregnancies following sterilization, the risk  
22 of ectopic pregnancy is high. The risk of pregnancy and  
23 the risk of only ectopic pregnancy was similarly associated  
24 with sterilization method, age at sterilization, and  
25 race/ethnicity.

1           In conclusion, all women and especially younger  
2 women undergoing tubal sterilization should be informed  
3 that pregnancy can occur following tubal sterilization and  
4 it can occur several years after the sterilization. Women  
5 should also know that if a pregnancy occurs, there is a  
6 high risk that it could be ectopic.

7           Thank you.

8           DR. BLANCO: Thank you very much.

9           At this point, these are all the presenters  
10 that we have listed. Is there anyone in the audience who  
11 would like to make some brief remarks before the panel at  
12 this point?

13           (No response.)

14           DR. BLANCO: Okay. Having there not been  
15 anyone, at this point, we'll go ahead and move on with the  
16 agenda. I'd like to at this time bring back Mr. Colin  
17 Pollard for some initial comments about the next topic that  
18 we'll be dealing with.

19           MR. POLLARD: Thank you, Dr. Blanco, members of  
20 the panel, distinguished audience.

21           FDA has convened this meeting today to obtain  
22 input from you as independent experts and members of this  
23 panel. FDA will use your recommendation as it moves  
24 forward with the review of this PMA application for the  
25 Essure Micro-Insert, a hysteroscopically-delivered implant

1 for permanent female sterilization.

2 I'd like to make several points, as you begin  
3 your day on this PMA. First, as Dr. Whang, your panel  
4 executive secretary will go over with you later today, your  
5 recommendation can take one of three forms -- approvable,  
6 approvable with conditions, or not approvable -- and for  
7 the latter two possibilities, we will expect the panel to  
8 provide details on how to make the PMA approvable.

9 Secondly, there are three key operative  
10 definitions that apply to the review of PMAs: valid  
11 scientific evidence, safety, and effectiveness. I won't go  
12 over the definitions with you now. We'll do that later.  
13 They are given in your folder and I suggest you take a  
14 quick look to refresh your memory. When we introduce the  
15 panel discussion questions in the afternoon, we'll read the  
16 definitions out loud.

17 You have before you today the premarket  
18 approval application for a hysteroscopically-delivered  
19 implant that is placed in the fallopian tubes of women who  
20 intend to be permanently sterilized. By way of a little  
21 history, about 10 years ago, starting in the late '80s,  
22 this panel reviewed three other PMAs which FDA went on to  
23 approve for tubal occlusion devices that are placed  
24 laparoscopically. Two of these three devices were so-  
25 called preamendments devices. That is, they were on the

1 market before enactment of the 1976 Medical Device  
2 Amendments. All three PMAs were for devices that had a  
3 great deal of market experience and were supported by a  
4 wide variety of devices from the published literature, and  
5 at each of the three panel meetings for those PMAs, we were  
6 fortunate as we are today to have a representative from the  
7 Centers for Disease Control to discuss what is probably the  
8 definitive longitudinal study of female sterilization, the  
9 prospective multicenter Collaborative Review of  
10 Sterilization, the so-called CREST Study. I want to thank  
11 Dr. Costello for giving us a very nice overview of that  
12 study. Results from this study have been useful to help  
13 put the safety and effectiveness of such devices into  
14 perspective.

15 My next to last point is that this PMA before  
16 you today represents the next generation of devices for  
17 female sterilization with advancements in the technology.  
18 While this device does not have the extensive clinical  
19 experience of the earlier devices, it is supported by the  
20 results from a series of studies on which the sponsor  
21 embarked after substantial consultation with the agency.  
22 This will make some aspects of the review a little more  
23 difficult and we will give you a little bit more  
24 information on that later.

25 And lastly, I should note that nowadays, FDA

1 does not take every single PMA we receive before the panel,  
2 only first-of-a-kind devices or when difficult clinical  
3 issues are raised. This device is the first  
4 hysteroscopically-delivered sterilization device and that  
5 is why we have brought it before you. This PMA, the  
6 results of your deliberations and ultimately our decision  
7 will serve as a model for review of future PMAs of like  
8 devices.

9 Thank you in advance for your careful attention  
10 to the details of the PMA. We look forward to your  
11 discussion.

12 Any questions?

13 (No response.)

14 DR. BLANCO: Thank you, Mr. Pollard.

15 At this time, I'd like to go ahead and begin  
16 the presentation by the sponsor, and I'd like to introduce  
17 Cindy Domecus from the Conceptus Corporation to begin the  
18 presentation and introduce the rest of the speakers.

19 Welcome back.

20 MS. DOMECUS: Good morning.

21 Distinguished panel, FDA and interested public,  
22 we are pleased to present to you today a summary of the PMA  
23 for the Essure System. My name is Cindy Domecus, and I'm  
24 the Senior Vice President of Clinical Research and  
25 Regulatory Affairs at Conceptus.

1           At the outset of our presentation, we would  
2     like to publicly acknowledge the FDA for all the valuable  
3     input we have received from them during each stage of our  
4     clinical evaluations. Our first clinical evaluations began  
5     in 1996 with the earlier design iterations of the device  
6     and we sincerely thank FDA for its guidance during the past  
7     six years of clinical research.

8           After introducing the other members of our  
9     panel presentation team, I will briefly review the public  
10    health issues that motivated Conceptus to develop an  
11    alternative contraceptive option for women. Next, we will  
12    describe the device, its mechanism of action, and we'll  
13    provide an overview of the Micro-Insert placement  
14    procedure. Following that, I will provide an overview of  
15    the four clinical trials that were conducted in support of  
16    the Essure System PMA. We will then highlight the results  
17    from the pre hysterectomy study and pivotal trials. We will  
18    conclude our presentation by addressing each one of the  
19    panel discussion questions today. So that we can stay  
20    within the allotted time frame for our presentation, we  
21    respectfully request that you hold questions until the  
22    completion of our presentation.

23           I would now like to introduce to you the other  
24    members of the panel presentation team. First, Dr. Jay  
25    Cooper, who is the principal U.S. investigator for the

1 pivotal trial. He will speak to you today regarding the  
2 device description and mechanism of action and will also  
3 provide an overview of the Micro-Insert placement  
4 procedure.

5 Dr. Thomas Wright, who is an independent  
6 histopathologist for the entire project, will speak to you  
7 today regarding the prehisterectomy study results.

8 Dr. Charles Carignan, who is Vice President of  
9 Clinical Research and Regulatory Affairs at Conceptus, will  
10 present to you the results from the pivotal trial.

11 Conceptus chose to develop Essure because of  
12 what we believe to be a clear need for contraceptive  
13 alternatives for women. This need is evidenced by the high  
14 unintended pregnancy rate in the United States. Based on  
15 data from the most recent cycles of the National Survey of  
16 Family Growth, it is estimated that almost half of the  
17 pregnancies in the United States are unintended. It has  
18 been suggested in the literature that the high unintended  
19 pregnancy rate is due to dissatisfaction and imperfect use  
20 with reversible methods.

21 Currently, women must choose between reversible  
22 birth control methods associated with these high unintended  
23 pregnancy rates and permanent methods which require  
24 invasion of the abdominal cavity, typically under general  
25 anesthesia. Although permanent methods of birth control

1 are associated with very high effectiveness rates, they are  
2 not without significant risk. As published by Jamieson, et  
3 al., tubal sterilization performed via laparoscopy is  
4 associated with a 1.6 percent major complication rate.  
5 Layde, et al., reported 5.7 percent major complication rate  
6 when tubal sterilization is performed via laparotomy. Of  
7 note, Destefano, et al., reported a fivefold decrease in  
8 complication rates when tubal sterilization is performed  
9 with local instead of general anesthesia. These risks are  
10 made more significant by the fact that tubal sterilization  
11 is the most prevalent form of birth control in the United  
12 States. The vast majority of the major complications with  
13 the transabdominal approach are due to incisions, blind  
14 insertion of instruments into the abdomen, and general  
15 anesthesia. Conceptus chose to develop a transcervical  
16 approach to tubal sterilization in order to avoid the risks  
17 associated with these characteristics of a transabdominal  
18 approach.

19 I will now turn the podium over to Dr. Jay  
20 Cooper, the principal U.S. investigator, who will present  
21 to you a description of the device, its mechanism of  
22 action, and will provide an overview of the Micro-Insert  
23 placement procedure.

24 Before Dr. Cooper speaks, however, Colin will  
25 pass out to you some samples of the device. We have it in

1 two forms, the Micro-Insert provided in a vial and the  
2 Micro-Insert contained within its delivery system provided  
3 in a pouch. I'll ask that Colin pass those out now, and  
4 we'll have a few minutes to handle the device before Dr.  
5 Cooper speaks to you. Just for the record, it's more than  
6 fine for you to open the packages and we actually would  
7 encourage you to handle the Micro-Insert itself so you can  
8 see its soft flexible nature.

9 DR. COOPER: As is being done here by Dr.  
10 Noller, you can take the catheter guide assembly system,  
11 the plastic tubing, so you can get a much better idea of  
12 the entire system.

13 Dr. Blanco, shall I proceed?

14 DR. BLANCO: Yes, please.

15 DR. COOPER: Thank you. Thank you, Cindy, and  
16 thank you to the FDA, the distinguished panel, for the  
17 opportunity to be here this morning and to speak to you  
18 regarding Conceptus' application for PMA approval.

19 I have worked with Conceptus as a medical  
20 advisor in the refinement and clinical evaluation of  
21 various iterations of the Essure device and have served as  
22 the principal investigator in the North American clinical  
23 trial of the Essure device. As such, I have received  
24 compensation which now represents a financial interest in  
25 the company.

1           As the panel members can now attest, the Essure  
2   Micro-Insert is both soft and flexible. It is four  
3   centimeters in length. It is composed of a narrow inner  
4   coil and an outer coil of larger diameter. Laced along the  
5   length of the intercoil is a weave of PET fibers. At full  
6   expansion, the outer coil can achieve a diameter as great  
7   as two millimeters. The leading edge of the device has a  
8   ball-tipped swelling which facilitates the forward  
9   advancement and proper placement of the device into the  
10   proximal fallopian tube.

11           The Essure device is radiopaque and on a simple  
12   flat plate x-ray of the pelvis can be seen to conform in  
13   shape to the natural curvature of a woman's fallopian  
14   tubes. The Essure System is composed of a handle and  
15   guide wire and coaxial catheter assembly system that allows  
16   for one-handed placement and deployment of the Micro-Insert  
17   into the proximal fallopian tube. The ergonomically  
18   designed handle makes use of a rotatable thumb wheel and  
19   gear system which provides for retraction first of the  
20   outer delivery catheter and next withdrawal of the  
21   interrelease catheter, allowing the Micro-Insert to be  
22   fully deployed.

23           Because the outer delivery catheter is only one  
24   millimeter in diameter, it can easily be passed through a  
25   five-fringed operating channel of any commercially

1 available hysteroscope. Using sequential photographs, the  
2 key components of the Essure Micro-Insert and catheter  
3 assembly can be seen. The delivery catheter has several  
4 unique properties which aid the operator in proper device  
5 deployment. The catheter is hydrophilic, allowing it to  
6 become slippery and lubricated as it passes through the  
7 saline-filled uterine cavity. The catheter wall thickness  
8 provides appropriate column strength for slow advancement  
9 into and through the tubal lumen. Approximately two  
10 centimeters from the leading edge of the catheter is a  
11 black positioning bump. When this positioning bump is seen  
12 by the hysteroscopist to advance to the tubal ostium, the  
13 operator is certain that the underlying Micro-Insert still  
14 wound down and constrained by the release catheter is now  
15 properly positioned.

16 If you would, imagine this line running from  
17 this black bump right down here. To your right represents  
18 what's happening in the patient's fallopian tube. To your  
19 left represents the uterine cavity. So we see now in this  
20 photograph that the delivery catheter has been withdrawn  
21 back into the operating channel of the hysteroscope. The  
22 distal portion of the device can be seen at the tubal  
23 ostium still constrained and wound down. The orange  
24 releases catheter has not yet been released.

25 In the next photograph, the release catheter

1 has been withdrawn, the device is now free to expand to its  
2 maximum diameter. The operator can see four or five of  
3 these microcoils at the uterine cornua, and finally, in the  
4 last image, the guide wire has been separated away from the  
5 device, leaving it free and properly positioned at the  
6 utero-tubal junction and spanning the intramural portion of  
7 a fallopian tube.

8 This schematic illustrates the ability of the  
9 Essure device to assume a greater diameter at the tubal  
10 ostium and in the proximal fallopian tube than it can in  
11 the intramural portion of the fallopian tube. The thick  
12 musculature of the uterus prevents the device from assuming  
13 its maximum diameter. It is this unique and dynamic  
14 property of the Essure device that explains its ability to  
15 accommodate to variable tubal widths and also explains its  
16 exceptionally high rate of acute and long-term retention.

17 There is a threefold explanation for the  
18 mechanism of action for the Essure device. Expansion of  
19 the outer coil for acute anchoring, space-filling and  
20 mechanical blockage of the tubal lumen, and finally tubal  
21 occlusion by tissue ingrowth into and around the Micro-  
22 Insert from the tubal mucosa.

23 Next, I'd like to show you an animation of the  
24 procedure being performed. The hysteroscope will be placed  
25 into the uterus. The left tubal ostium will be identified.

1     Scope is in place. The guide assembly catheter system is  
2     being passed through the hysteroscope, now it's passed into  
3     the fallopian tube to the black positioning bump. A  
4     catheter is withdrawn, the wound-down device will be  
5     released as the release catheter is pulled away. The  
6     device now is fully deployed. The guide wire is disengaged  
7     from the device and the device remains in this position  
8     spanning the utero-tubal junction with just a few of the  
9     microcoils seen in the uterus by the hysteroscopist.

10           Having seen an animation of the device  
11     placement procedure, I think it is easier for us to better  
12     appreciate the key steps in device placement as viewed  
13     through the hysteroscope. With the uterus distended with  
14     saline, both tubal ostia are visualized. In this  
15     situation, we see the left tubal ostium in the center of  
16     our visual field. In the next image, we see that the  
17     delivery catheter has been advanced into the uterus, into  
18     the fallopian tube, to the position of the black  
19     positioning bump. In the next image, the delivery catheter  
20     has been withdrawn away from the underlying device. The  
21     device remains in a wound-down state and the release  
22     catheter can be seen at the periphery of the image.

23           In the next image, the orange release catheter  
24     is no longer in view because it has been pulled away or  
25     released from the device. Now the device is allowed to

1 spring to life, so to speak, to assume its full diameter  
2 and all that remains in the next image is to disengage the  
3 guide wire from the device. Here, the guide wire is being  
4 rotated in a counterclockwise fashion using the handle, and  
5 finally we see the device at the left tubal ostium fully  
6 deployed.

7 Owing to my experience as the principal  
8 investigator in the pivotal trial and having the  
9 opportunity to observe physicians as they began their  
10 experience with the Essure System, it is my view that this  
11 procedure should be seen as the simplest of operative  
12 hysteroscopic procedures. Performed with a hysteroscope  
13 similar to that used in diagnostic evaluations, the Essure  
14 procedure is devoid of many of the risks and concerns  
15 associated with advanced operative hysteroscopic  
16 procedures. Cervical dilation is most often not required  
17 and if so is limited to 5.5 millimeters. Physiologic  
18 saline is used for distention of the uterine cavity as  
19 opposed to non-physiologic solutions, such as glycine or  
20 sorbitol. The risk of fluid intravestation is minimized as  
21 uterine distension pressures are controlled by gravity feed  
22 and there is no cutting or resection of endometrial tissue.  
23 Electrosurgery is not employed. The procedure is  
24 considerably more rapid than is the typical operative  
25 hysteroscopic procedure and intraoperative bleeding is

1 extremely uncommon.

2 Thank you for your attention, and I will turn  
3 the program back to Cindy.

4 DR. BLANCO: Thank you.

5 MS. DOMECUS: Thank you, Dr. Cooper.

6 I will now introduce the next section of our  
7 presentation with an overview of the four clinical trials  
8 that Conceptus conducted in support of the Essure System  
9 PMA.

10 After two years of clinical testing with the  
11 earlier device iterations, clinical testing of the gamma  
12 design began in 1998, with testing in hysterectomy patients  
13 to obtain data on the feasibility of device placement.  
14 Over 40 women were enrolled into this study and the data  
15 from this study supported moving into the next stage of  
16 clinical testing. At the next stage, the Micro-Insert  
17 placement was performed in hysterectomy patients 1 to 30  
18 weeks prior to a planned hysterectomy. This study yielded  
19 the first data on Micro-Insert placement in awake women as  
20 well as the first data on the safety and comfort of the  
21 implanted Micro-Insert. This study also provided  
22 histological data to support the theorized mechanism of  
23 action. Over 60 women were enrolled into this study.

24 A Phase II study of safety and effectiveness in  
25 sterilization candidates was also conducted. This study

1 provided the first safety and effectiveness data in the  
2 intended patient population and over 200 women were  
3 enrolled into this study. Finally, based on the  
4 encouraging results from the Phase II study, a pivotal  
5 trial was initiated in the year 2000 after extensive  
6 discussions with the FDA regarding study design. Over 500  
7 women were enrolled into this study. In summary, as you  
8 can see, clinical testing of the current product has  
9 involved over 850 women spanning over a four-year period.

10 Dr. Wright will now present to you the results  
11 from the pre hysterectomy study, followed by Dr. Carignan  
12 who will present to you the results from the pivotal trial.

13 DR. WRIGHT: Good morning.

14 Before I describe the results of the  
15 pre hysterectomy study, I would like to disclose that I was  
16 paid as a consultant by Conceptus to perform the  
17 histopathological analysis of specimens from the  
18 pre hysterectomy study. I have no other financial interest  
19 in Conceptus.

20 Next slide.

21 The pre hysterectomy study enrolled women  
22 requiring a hysterectomy for a variety of gynecological  
23 reasons. These women underwent placement of the Micro-  
24 Insert 1 to 30 weeks prior to hysterectomy and underwent a  
25 hysterosalpingogram one week prior to undergoing the

1 hysterectomy. Immediately after the hysterectomy was  
2 performed, the cornual regions of the uterus, together with  
3 the fallopian tube, were removed from the uterus and sent  
4 to a central pathology laboratory for specialized  
5 processing. This involved embedding the entire section of  
6 tube together with the device in situ into plastic. The  
7 embedded tube and device were then cut into sections which  
8 were ground down to an appropriate thickness for  
9 microscopic assessment using a diamond-grinding wheel.  
10 This allowed us to look at the relationship between the  
11 tissue, the fallopian tube and the device.

12 Histopathological sections were all evaluated by a single  
13 blinded pathologist to wearing time and all clinical  
14 information.

15           Next. These are the results obtained on the  
16 hysterosalpingograms that were obtained one week prior to  
17 the hysterectomy. A total of 51 women wore the device  
18 between 1 and 30 weeks. Most women had devices in place  
19 between 4 and 14 weeks. All 51 women, including the five  
20 women who wore the device for less than four weeks, showed  
21 100 percent occlusion by hysterosalpingogram.

22           Next. This microscopic view shows a cross-  
23 section of a fallopian tube with the device in place. It  
24 was obtained from the patient who wore the device for four  
25 weeks. Both the intercoil, which you can see here, and the

1 outer coil are visible. This is a smooth muscle of the  
2 tube out in the periphery. Even after only four weeks of  
3 wearing time, the dense fibrosis, which is seen as a golden  
4 brown staining seen there, has developed between the inner  
5 and the outer coils. The normal tubal architecture is  
6 completely disrupted and we have here almost total  
7 occlusion.

8 The region of loose fibrosis which is  
9 immediately adjacent to the inner coil which you see right  
10 here is the area that contains the bulk of the PET fibers.  
11 The apparent space between this area of loose fibrosis and  
12 the denser fibrosis is probably an artifact of the  
13 processing and the methylocrylate bedding and the diamond  
14 knife grinding.

15 Next. This cross-section was obtained from a  
16 patient who had the device present for 13 weeks. Again,  
17 you can see both the inner and the outer coil, and the  
18 lumen appears to be almost totally occluded by dense and by  
19 loose fibrosis. In addition, you can see here some smooth  
20 muscle cells which appear to have migrated in from the wall  
21 of the tube into the space between the inner and the outer  
22 coil. You can also see here that the inner coil in this  
23 cross-section is occluded by loose fibrous tissue.

24 Next. This is a higher magnification of that  
25 same section. I'm showing this to show the PET fibers

1 present between the inner and the outer coil. You can see  
2 the multinucleated giant cells which are typically seen in  
3 association with the PET fibers together with the fibrosis.  
4 This sort of appearance is very typical of what we see with  
5 PET fibers when they are used in a variety of other devices  
6 and vascular grafts in other body systems, this sort of  
7 elicitation of a dense fibrosis together with an  
8 inflammatory infiltrate.

9 Next. Key histological features observed in  
10 the sections were graded in a blinded fashion. Over time,  
11 we observed an increase in the amount of dense fibrosis  
12 which is shown in the yellow line and a reduction in the  
13 amount of acute inflammation which is shown in the white  
14 line. Both chronic inflammation and loose fibrosis  
15 appeared relatively stable up to a 15-week period of  
16 looking at these devices.

17 In conclusion, the pre hysterectomy study has  
18 shown total tubal occlusion by hysterosalpingograms in all  
19 of the participants at all of the time points, including  
20 even those women who wore the device for less than four  
21 weeks. The histological studies have shown that the tissue  
22 response to the device is predictable and is progressive.  
23 It is occlusive in nature and it produces a dense fibrosis.

24 Finally, the tissue response is quite  
25 localized. Sections from the tubes taken approximately

1 five millimeters distal to where the device was showed a  
2 normal tubal architecture and there was no evidence that  
3 the reaction to the device extended out to the serosal  
4 surfaces of the tube. So the reaction was confined to the  
5 area around the device.

6 Thank you very much. I would now like to  
7 present Chuck Carignan who will continue with the  
8 presentation.

9 DR. CARIGNAN: Thank you, Dr. Wright. Thank  
10 you, members of the panel.

11 I'm Dr. Charles Carignan, vice president of  
12 clinical research and medical affairs for Conceptus, and  
13 I'd like to thank you for the opportunity to share with you  
14 the results of our pivotal trial.

15 The objectives of the pivotal trial were to  
16 evaluate the safety and participants' tolerance of and  
17 recovery from the Essure placement procedure, the safety  
18 and tolerance to the implanted Micro-Inserts, tubal  
19 occlusion by HSG at three months, and the effectiveness in  
20 preventing pregnancy with the primary endpoint being  
21 effectiveness at one year.

22 Women were followed up at one week and three  
23 months following device placement when they were relying on  
24 alternative contraception. She was then followed up at  
25 three, six and 12 months after she began relying on Essure

1 as her sole method of contraception and Years 2 through 5  
2 are being conducted under postmarket surveillance. The  
3 one-year results are presented here today.

4 The average age of the women in the pivotal  
5 trial was 32 with an age range of 21 to 40 and consistent  
6 with the study design, nearly two-thirds of the women were  
7 age 33 and younger and one-third were age 34 and older.  
8 There were 13 clinical trial sites with eight of the sites  
9 located in the U.S., two in Australia, and three in Europe,  
10 and the majority of women were enrolled in the United  
11 States.

12 This is a summary patient tree of the handouts  
13 that you all received. Five-hundred eighteen women  
14 initially underwent hysteroscopy but 11 women were found  
15 not to have identifiable tubia ostia. Five-hundred seven  
16 women actually underwent the Essure procedure, with 464  
17 achieving bilateral placement and two had placement in a  
18 unicornuate uterus. Four-hundred forty-nine women  
19 ultimately began relying on Essure, 446 with satisfactory  
20 device location and occlusion, and three women began  
21 reliance without undergoing an HSG. Twelve women were  
22 noted to have unsatisfactory device location on the three-  
23 month post-device placement and three women were lost to  
24 follow-up after device placement. As of May 24th, we had  
25 408 women completing the one-year follow-up, 14 women who

1 were lost to follow-up after beginning reliance, and 27  
2 women who were still awaiting a one-year visit.

3 Ninety-two percent of women achieved bilateral  
4 placement with 88 percent achieving so on a first procedure  
5 and 4 percent of women requiring a second procedure to  
6 achieve bilateral placement. Of the 41 women not achieving  
7 bilateral placement, 23 did not undergo a  
8 hysterosalpingogram after failing placement. However, of  
9 the 18 women who did undergo a follow-up  
10 hysterosalpingogram, 15 or 83 percent were found to have  
11 proximal tubal occlusion which would explain their  
12 inability to achieve device placement and only three women  
13 who failed placement were found to have patent tubes.

14 On the day of device placement, adverse events  
15 were noted in only 3 percent of women and all adverse  
16 events resolved prior to discharge. None required major  
17 surgery and there were no hospitalizations with the  
18 exception of one woman who was observed overnight due to an  
19 adverse reaction to pain medication she received in the  
20 recovery area.

21 There were Micro-Insert perforations at a rate  
22 of 1 percent and there no symptoms among those experiencing  
23 perforation. The majority of women reported no to mild  
24 pain during the procedure, most describing it as period-  
25 type pain. Eighty-two percent of women received a

1 nonsteroidal antiinflammatory drug prior to the procedure  
2 to reduce uterine cramping and tubal spasm.

3 When looking at predominant anesthesia and  
4 predominant anesthesia is that which has a higher order of  
5 anesthetic effect, you can see that 52 percent of women  
6 received local anesthesia alone as a pericervical block and  
7 41 percent received IV sedation or analgesia. Only one  
8 woman in the pivotal trial received general anesthesia and  
9 that was at her request. With this low level of  
10 anesthesia, 88 percent of women rated their tolerance of  
11 the procedure as excellent to good.

12 The average time to discharge was 45 minutes.  
13 There were no immediate post-procedure events in 58 percent  
14 of women and those experiencing an event, the most frequent  
15 were cramping, pain and nausea. As I mentioned, all were  
16 resolved prior to discharge. There was no post-procedural  
17 analgesia required in 75 percent of the women. Of the 329  
18 women who were employed in the study, 74 percent reported  
19 missing less than one day of work following the day of the  
20 procedure and an additional 18 percent missed one day of  
21 work.

22 At the three-month post-device placement visit,  
23 women underwent a hysterosalpingogram to determine device  
24 location and occlusion. They also had a pelvic exam and  
25 office visit to answer questions regarding comfort and

1 satisfaction. If the woman had satisfactory location and  
2 occlusion, she discontinued alternative contraception and  
3 began relying on Essure. Ninety-seven percent of women  
4 were ultimately able to rely on Essure as their sole method  
5 of contraception. Three women or 0.6 percent were lost to  
6 follow-up and 12 women or 2.6 percent experienced an  
7 adverse event that prevented them from relying. Those  
8 adverse events were expulsion, perforation or other  
9 unsatisfactory device locations.

10 Micro-Insert-wearing data was collected at  
11 three, six, and 12 months of reliance. Women were asked  
12 about their comfort and satisfaction with Essure and were  
13 asked whether or not they had experienced even a single  
14 episode of unusual pain or bleeding as well as any adverse  
15 changes in health that they experienced.

16 As can be seen here, at all study visits,  
17 comfort with Essure has been rated very high, with comfort  
18 at one year rated as excellent in more than 90 percent of  
19 women. Again, women were asked at each study visit if they  
20 had experienced any unusual pain since the last contact.  
21 Pelvic pain was categorized as dysmenorrhea, dyspareunia,  
22 ovulatory pain, or other pelvic pain. Only 3 percent of  
23 women reported such episodes of pain at more than one study  
24 visit and only one woman reported episodes of pelvic pain  
25 at every study visit.

1           Women were also asked about any episodes of  
2   irregular bleeding at each study visit. Reports were then  
3   categorized as irregular menses, spotting or intermenstrual  
4   bleeding or changes in menstrual flow. Few women reported  
5   persistent changes in menstrual flow while some women  
6   reported transient menstrual changes. Of the women with  
7   persistent changes, two women reported persistent  
8   intermenstrual bleeding, nine women reported an increase in  
9   menstrual flow, while eight women reported a decrease in  
10   menstrual flow. All of the menstrual function changes and  
11   pelvic pain have to be considered in light of the fact that  
12   48 percent of women discontinued the use of oral  
13   contraceptives after the alternative contraception period.

14           Adverse events were defined as any untoward  
15   deviation from baseline health. Daily diaries were  
16   maintained by the study participants for six months.  
17   Investigators were also prompted by case report forms at  
18   each study visit on two separate questions, in addition to  
19   the questions on pain and bleeding on the case report  
20   forms. It should be noted that multiple episodes of the  
21   same complaint from the same woman are counted as multiple  
22   adverse events. So for example, one woman in the pivotal  
23   trial reported six episodes of low back pain at her three-  
24   month post-device placement visit. That is reflected as  
25   six events in the adverse events by body system table that

1 I will show you next. The adverse events by body system  
2 table reports all events in each category that were related  
3 as possible, probable or definitely related to the device.

4 This table shows the number of events reported  
5 and the number that you can see here, the most frequent  
6 were low back pain, abdominal pain or cramps, and  
7 dyspareunia. Only eight events were rated as definitely  
8 related to the Essure device. The reports of pain,  
9 bleeding and adverse events are kept in perspective when  
10 looking at satisfaction with Essure. From the three-month  
11 post-device placement visit onward, more than 90 percent of  
12 women rated their satisfaction with Essure as very  
13 satisfied.

14 There were no reported pregnancies in women  
15 relying on Essure in the pivotal trial. However, it should  
16 be noted that there were four luteal-based pregnancies that  
17 occurred prior to device placement but were diagnosed after  
18 device placement. The current estimate of the first-year  
19 effectiveness rate based on the pivotal trial data alone is  
20 100 percent with a 95 percent confidence interval of 99.31  
21 to 100 percent. There were also no reported pregnancies in  
22 women relying on Essure during the Phase II study, with the  
23 exception of a woman using an earlier device iteration, the  
24 Beta design, who became pregnant. However, that design was  
25 discontinued in 1998 and is not the subject of this PMA.

1 Combining the Phase II and pivotal trial one-year follow-up  
2 results in a combined one-year effectiveness rate of 100  
3 percent with a 95 percent confidence interval of 99.52 to  
4 100 percent.

5 So in conclusion, in the pivotal trial, Essure  
6 was demonstrated to be highly effective with a very high  
7 patient satisfaction, a well-tolerated placement procedure,  
8 a rapid return to work and normal activities. It was shown  
9 to be comfortable and safe without the requirement for  
10 general anesthesia or for incisions.

11 Thank you.

12 MS. DOMECUS: Thank you, Dr. Carignan.

13 I will now conclude our presentation with a few  
14 slides to address the questions put before the panel today  
15 for discussion.

16 Question Number 1 before the panel asks about  
17 the effectiveness rate of Essure in comparison to other  
18 methods of female sterilization. Plotted on this graph are  
19 the point estimates and the confidence intervals shown by  
20 the white lines for the failure rates of various methods  
21 during the first year. These rates are based on the CREST  
22 Study and published literature on the Filshie clip since  
23 the Filshie clip was not part of the CREST Study. As you  
24 can see, both the unadjusted and age-adjusted failure rates  
25 for Essure compare quite favorably with the other methods

1 of tubal sterilization.

2 This graph is the same as the prior graph but  
3 presents the second-year failure rates. It doesn't include  
4 data on the Filshie clip, however, since second-year  
5 failure rates on the Filshie clip cannot be calculated  
6 based on published literature. As you can see, the point  
7 estimate of the second-year failure rate for Essure is 0  
8 percent. The size of the confidence intervals is due to  
9 the sample size of 149 women completing the two-year  
10 visits. It should be noted, however, that the primary  
11 endpoint for the pivotal trial was the effectiveness rate  
12 at one year and the two-year data is being provided as a  
13 supplementary endpoint.

14 Question Number 2 asked the panel about the age  
15 distribution in the CREST Study as compared to the Essure  
16 pivotal trial. This question compares the age distribution  
17 based on three age groups. However, it should be pointed  
18 out that the pivotal trial study design was based on two  
19 age groups, those under the age of 34 and those 34 to 40.  
20 As can be seen, the distribution among these two age groups  
21 was quite similar between the two studies. The pivotal  
22 trial was not designed to enroll an equal percentage of  
23 patients to that of the CREST Study in the age group of 18  
24 to 27 since there was no statistically significant  
25 difference in the failure rates of this age group compared

1 to the next oldest age group of women age 28 to 33. Also,  
2 the CREST Study showed the regret was highest among this  
3 youngest age group. Finally, natural fertility has been  
4 shown to decrease after the age of 34. Therefore, we  
5 focused on only these two age groups. Finally, of note is  
6 that the age cap in the pivotal trial was 40 years of age  
7 compared to 44 years of age in the CREST Study.

8 Question Number 3 asks about the likelihood of  
9 recanalization in the long-term setting. First, it should  
10 be pointed out that there's currently no evidence of long-  
11 term failures with Essure. As of the last update to the  
12 PMA, there are 281 women who have successfully relied on  
13 Essure for contraception for 18 months, 149 women who have  
14 successfully relied on Essure for 24 months, and five who  
15 have relied on Essure successfully for 36 months.

16 In addition to the data on Essure, there's a  
17 long history with the use of PET fibers and implant  
18 indications, such as cardiac valves, stents, and grafts.  
19 PET fibers consistently produce a durable, dense, fibrotic  
20 response and therefore we believe that the likelihood of  
21 recanalization with Essure is quite low. Importantly, the  
22 device was designed to include a minimum 1.2 centimeter  
23 section of the fallopian tube, including the entire  
24 intramural section, which should also decrease any risk for  
25 recanalization.

1           Finally, as will be discussed on a later slide  
2   regarding postmarket surveillance, both the Phase II and  
3   pivotal trials will follow patients to five years and  
4   there's already a commitment to provide the FDA with this  
5   data under postmarket surveillance.

6           Question Number 4 asks the panel about the  
7   adequacy of our plan to require a pelvic x-ray instead of  
8   HSG to evaluate Micro-Insert location and retention. We  
9   believe that our plan is adequate for the following  
10   reasons. First, all of the unsatisfactory Micro-Insert  
11   locations could be detected on pelvic x-ray alone. Second,  
12   the patency rate observed in the Essure clinical trials is  
13   quite similar to the patency rate published in the  
14   literature when HSGs have been performed subsequent to  
15   tubal sterilization.

16           Finally, we would like to point out that the  
17   performance of the follow-up HSG is not the standard of  
18   care for tubal sterilization and neither is pelvic x-ray.  
19   In that light, we think that our plan is more than adequate  
20   and is actually quite conservative.

21           Question Number 5 asks about the acceptability  
22   of the placement failure rate. First, as shown previously  
23   in Dr. Carignan's presentation, it should be noted that 83  
24   percent of the evaluated placement failures were  
25   attributable to proximal tubal occlusion. While such

1 patients are reflected in the placement failure rates for  
2 Essure, they are not even identified with the  
3 transabdominal approach. Also, when evaluating the risk of  
4 placement failure, one must consider the fact that the  
5 placement procedure is well-tolerated by the vast majority  
6 of patients and is associated with minimal risks.

7 It is noteworthy that the high placement rates  
8 were achieved in both obese women and in women with a  
9 history of prior abdominal or pelvic surgery. This is of  
10 great importance because these very women are often refused  
11 laparoscopic tubal ligation because of increased risk of  
12 intraoperative complications. It is also important to note  
13 that placement failure does not preclude subsequent  
14 treatment.

15 Finally, we believe that offering women a less-  
16 invasive approach to permanent birth control prior to a  
17 more-invasive transabdominal procedure is consistent with  
18 common clinical practice in other areas, such as the  
19 performance of angioplasty prior to coronary artery bypass  
20 graft or laparoscopic prior to cholecystectomy.

21 I will not address Question Number 6 regarding  
22 the safety of the placement procedure since that was  
23 already covered by Dr. Carignan's presentation.

24 Question Number 7 is regarding the adequacy of  
25 our proposed training program which I will briefly review

1 here. First, I would like to point out that this training  
2 program was developed by Conceptus with significant input  
3 and oversight from our Medical Advisory Board. There are  
4 several components to the Essure Training Program.

5 First, a full-day course with didactic  
6 presentation and distribution of a training manual. This  
7 course is given only by trainers approved by the Conceptus  
8 Professional Education Department. Next, training is  
9 performed in a custom-designed Essure placement simulator  
10 which, unlike in vivo training, allows for placement  
11 practice in rapid succession. This simulator was developed  
12 to provide a surrogate for the perihysterectomy model. We  
13 have brought the simulator here today and are prepared to  
14 provide demonstration later, if the panel is so interested.

15 Training in the Essure placement simulator is  
16 then followed by preceptoring of initial cases. We plan to  
17 gather placement rate and adverse event data on all  
18 preceptored cases until formal sign-off using a  
19 standardized case report form. We expect preceptoring to  
20 average five cases. Finally, a technical help desk will be  
21 manned 24 hours a day seven days a week to provide ongoing  
22 training assistance. This training program is currently  
23 being used in Canada, Europe, Australia, and Singapore, and  
24 the next slide presents the data gathered using this  
25 training approach in the commercial setting.

1           Looking at the placement rates for the first 10  
2 cases conducted by the pivotal trial investigators, shown  
3 in blue, compared to the first 10 conducted in a commercial  
4 setting with this training approach, shown in orange, we  
5 see very similar placement rates. The approximate 4  
6 percent difference in the rates is likely due to the fact  
7 that at the time this analysis was conducted for submission  
8 in the PMA, the average number of procedures per physician  
9 in the commercial setting was less than half of that in the  
10 pivotal trial. We believe that this early data supports  
11 the validity of our proposed training approach and suggests  
12 that placement results seen in the pivotal trial are  
13 generalizable to the commercial setting.

14           The data from the pivotal trial were analyzed  
15 for learning curve using both placement rates and procedure  
16 time as markers. When looking at placement rates for the  
17 investigators that did not participate in the Phase II  
18 trial, placement rates were not significantly impacted  
19 after the first five cases. When looking at procedure  
20 times as a marker, we saw a continuous slight decrease in  
21 procedure time with experience. As another assessment of  
22 learning curve, investigators were asked to assess ease of  
23 use. The majority of investigators rated ease of use as  
24 simple or moderately simple. Based on these data, we  
25 believe that it is quite feasible for competency with the

1 procedure to be established after five cases and the  
2 procedure time should continue to decrease with experience.

3 Last, I would like to provide an overview of  
4 our postmarket surveillance plans. Both the Phase II and  
5 the pivotal trial protocols require women to be followed  
6 for five years. Also, both protocols request that Micro-  
7 Inserts and any surrounding tissue be returned to Conceptus  
8 for histological evaluation should a trial participant  
9 undergo future extrapative surgery of the reproductive  
10 organs for any reason. As mentioned earlier, we also  
11 intend to gather placement rate and adverse event data on  
12 all preceptored cases using a standardized case report  
13 form.

14 Finally, we will have a toll-free number for  
15 physicians to call regarding any adverse events and such  
16 events will fall under FDA regulations which already exist  
17 regarding complaint handling and reporting of certain  
18 events to FDA.

19 In conclusion, we believe that the data  
20 gathered to support the Essure System PMA represent valid  
21 scientific evidence in accordance with the FDA regulations  
22 that a reasonable assurance of safety and effectiveness has  
23 been established and that adequate training and postmarket  
24 surveillance plans are in place to support market release.  
25 We therefore respectfully request your recommendation for

1 approval today.

2 This concludes our presentation. Thank you for  
3 your attention. We'll be happy to answer any questions in  
4 the remainder of the day. I also wanted to point out that  
5 in addition to a copy of our presentation, we provided the  
6 panel with a letter from Dr. Barbara Levy, who cannot be  
7 here today but wanted to provide comments to the panel.

8 Thank you.

9 DR. BLANCO: Thank you very much for that very  
10 interesting nice presentation.

11 I'd like to go ahead. We're doing great on  
12 time. So if any of the panel members have any questions at  
13 this point, let's go ahead and let's try, rather than a  
14 discussion, since we're going to be discussing this  
15 afternoon, let's try to keep it to questions of fact, if  
16 you want something clarified, et cetera.

17 Go ahead. Go ahead, Dr. Brown.

18 DR. BROWN: Yes. Do you have any data in both  
19 the Phase II and pivotal trials about the racial and ethnic  
20 demographic mix of the patients on the trials?

21 MS. DOMECUS: Dr. Carignan is going to pull up  
22 that data for you. One moment.

23 DR. BLANCO: I might just suggest that if it's  
24 going to take awhile, maybe we can set that up and then  
25 bring that information back to the panel before we start

1 the discussion after we've had the other presentations in  
2 the interest of time. Does that seem reasonable? Okay.  
3 So if you all would look that up and see if you can find  
4 it, present it a little later on, we'll fit in.

5 Any other questions? Let's go ahead and finish  
6 with each individual. Dr. Brown, did you have anything  
7 else?

8 DR. BROWN: Yes. I also wanted specific  
9 numbers or percentages about patients with a history of  
10 prior pelvic surgery and history of pelvic inflammatory  
11 disease that were included in both of the trials.

12 DR. BLANCO: Okay. We'll go ahead and if you  
13 all would look those up.

14 Dr. Shirk?

15 DR. SHIRK: Cindy, one of the integral parts of  
16 this device is obviously the PET fibers. The panel didn't  
17 receive any data regarding the action of PET fibers. Could  
18 you guys sort of give us a biological effect? Obviously  
19 it's an integral part of equating the fibrotic effect of  
20 this, and I realize it's been used in multiple other  
21 devices, but again I'd like some information about the PET  
22 fibers.

23 DR. BLANCO: Anything else?

24 MS. DOMECUS: Can I clarify? You want more  
25 information about PET fibers?

1 DR. SHIRK: Yes.

2 MS. DOMECUS: Or the typical biological  
3 response to PET fibers?

4 DR. SHIRK: Well, the typical biological  
5 response.

6 MS. DOMECUS: Can I have Dr. Wright address  
7 that now or do you want to hold that?

8 DR. BLANCO: That would be fine. No, go ahead.

9 MS. DOMECUS: Dr. Wright?

10 DR. WRIGHT: PET fibers have a long history of  
11 being used in a variety of cardiac grafts and a variety of  
12 other prosthesis used in different body sites.

13 The response which you see to PET fibers is  
14 very well described in the literature. It consists of an  
15 acute and a chronic inflammatory infiltrate. Many times or  
16 typically you will see multinucleated giant cells become  
17 attracted to the PET fibers. The presence of the  
18 inflammation releases cytokines and chemokines which then  
19 induces an acute followed by a chronic inflammatory  
20 infiltrate.

21 One of the things that determines the exact  
22 type of response that you see with PET, at least in  
23 vascular grafts, is the weave of the meshes of the grafts.  
24 If you have a very tight weave, you tend to have less dense  
25 fibrosis going in. If you have a loose weave, such as what

1 we are seeing here, in the space between the inner and the  
2 outer coil, you've got a lot of inflammatory infiltrate,  
3 then you will get a dense fibrosis.

4 In systems that this event looked at over time,  
5 this response appears to be very durable in that it does  
6 not diminish, it remains as it is, and you maintain a  
7 chronic inflammatory infiltrate at the site of the fibers  
8 which is the way it remains as a durable fibrotic response.

9 Does that answer your question?

10 DR. SHIRK: Yes. I just wanted some  
11 information what the fibers were made out of and obviously  
12 it creates a chronic kind of inflammatory response?

13 DR. WRIGHT: An acute initially and then a  
14 chronic.

15 DR. SHIRK: During the patient's entire  
16 lifespan?

17 DR. WRIGHT: That's right, and with vascular  
18 grafts, we have long histories of patients who wear these  
19 for very long periods of time, showing that it does not  
20 cause adverse effects.

21 DR. BLANCO: Thank you.

22 DR. ROY: Could you just clarify something,  
23 though? I think one of the slides indicated that with  
24 chronicity of use, you had more dense adhesive process and  
25 less acute inflammatory process.

1 Does this mean that these fibers, once they are  
2 coated, then are no longer producing the sort of  
3 inflammatory reaction that would be characterized by the  
4 presence of the acute inflammatory cells?

5 DR. WRIGHT: This study, the pre hysterectomy  
6 study, was designed to look at very short time points.  
7 Almost all of the patients, except for one, had their  
8 uteruses removed within 16 weeks of placement. So it  
9 really is that period of time where you're going from acute  
10 to chronic inflammation.

11 From vascular graft work, when you look at  
12 vascular grafts taken 10 years after they have been in  
13 place, you see some acute and chronic inflammation  
14 associated with PET fibers. So it's a long-acting  
15 inflammatory response. The absolute amount of the acute  
16 response that I showed you appeared to be diminishing with  
17 each passing week. So I don't think it will totally go  
18 away. I think what you will see is a reduction compared to  
19 the acute responses at three and four weeks.

20 DR. ROY: But do the PET fibers themselves  
21 undergo some sort of deterioration or do they consistently  
22 persistently remain as a nidus for stimulating a reaction?

23 DR. WRIGHT: They remain as a nidus for  
24 stimulating reaction.

25 DR. BLANCO: Thank you.

1 DR. ROY: So I guess what we're all trying to  
2 get a sense of is, is there any pathologic or physiologic  
3 process that would suggest that the property of the PET  
4 fiber is subsequently lost or cleared and therefore that  
5 there could be the process of recanalization and hence lack  
6 of effect?

7 DR. WRIGHT: Right. The dense fibrosis that  
8 we're seeing here, together with the smooth muscle ingrowth  
9 in these sections, certainly based on the time lines that  
10 we've got which are out to in one patient out to 30 weeks,  
11 the rest of them out to 16 weeks, 15 point something,  
12 really shows that this appears to be a progressive  
13 response.

14 Once you replace that space by dense fibrosis  
15 together with some smooth muscles, to me, it's difficult to  
16 envision how that dense fibrosis would suddenly disappear  
17 and go away. I mean, that's not what we see with  
18 inflammatory reactions and repair reactions in other body  
19 systems. I mean, I assume that you would maintain a dense  
20 fibrosis. It would become occluded and unless there was  
21 some other force or inciting cause to cause it to break  
22 down or to cause a recanalization, I don't see how this  
23 dense fibrosis would become recanalized. It's also  
24 relatively long distance. The device is designed  
25 specifically to occlude 1.2 sonometer region which is a

1 relatively long region to undergo recanalization.

2 DR. ROY: The last concern would be, is there  
3 any reason for us to be wondering whether these giant cells  
4 that infiltrate this area or are produced are in any way  
5 precursors for a neoplastic process?

6 DR. WRIGHT: Right, and I didn't answer to  
7 that. It's the same sort. The pictures I showed you with  
8 giant cells could be from any vascular graft in the body,  
9 and we have a very long history of use of devices using PET  
10 fibers for long-term implants and they have been shown to  
11 be neoplastic.

12 DR. ROY: But those vascular grafts are  
13 typically in much older individuals and for reasonably  
14 shorter periods of time than what we're envisioning here.  
15 If we're anticipating the use of this as a sterilization  
16 process in women in their twenties who presumably and  
17 hopefully would live to their eighties, so is that  
18 differential time span a concern to someone such as  
19 yourself who's been involved in these investigations and  
20 processes?

21 DR. WRIGHT: That is not a concern to me,  
22 because I know of no data to suggest or to implicate PET  
23 for producing neoplasms long term, and in fact many of the  
24 implantable devices, such as cardiac valves which have PET  
25 as a dense mass around the valve rings which it's there in

1 order to suture into, are put into quite young, you know,  
2 children get cardiac valves which contain PET.

3 DR. ROY: Sure. Thank you very much.

4 DR. BLANCO: Thank you.

5 DR. SEIFER: I had a question, Dr. Wright, with  
6 regard to Dr. Roy's question, the first question about the  
7 histopathology that you've visualized at three months after  
8 placement of this and the mechanism by which it occurs.

9 Do you look at cross-sections of fallopian  
10 tubes after tubal ligation as well?

11 DR. WRIGHT: We look at tons of cross-sections  
12 of fallopian tubes.

13 DR. SEIFER: Okay.

14 DR. WRIGHT: Because it's a big GYN practice.  
15 We see many things which we think probably are post-tubal  
16 ligation just due to what we see on the histopathology.  
17 However, very rarely do we actually know that these are  
18 from patients who have had tubal ligations.

19 DR. SEIFER: Can you give us some information  
20 with regard to what happens when you have recanalization  
21 after tubal ligation by any of these six methods that were  
22 followed up in the CREST Study and how it might compare to  
23 the kind of pathology that you see after placement of this  
24 Essure device?

25 DR. WRIGHT: All right. That's a really good

1 question, and I actually have during the course of this  
2 study asked a number of GYN pathologists as I've come into  
3 contact with them about what is the pathology of  
4 recanalization of a fallopian tube and have they ever seen  
5 a case where they felt they could definitely say they had  
6 seen histopathological evidence of recanalization, and in  
7 fact nobody that I've spoken to, Chris Crum at the Brigham,  
8 people in New York, a variety of people, have ever seen  
9 things which they can tell me were truly recanalization of  
10 a fallopian tube.

11 Typically, the scenario where this occurs is in  
12 the patient who presents with an ectopic pregnancy, and in  
13 that case, the tube has got such dramatic tubal damage,  
14 dilatation, hematosalpinx, all the things which go along  
15 with the ectopic, that you really don't see an area which  
16 you are sure has been recanalized in that preexisting tube.

17 What I can tell you, though, and this I feel  
18 very comfortable about, is that the degree of occlusion and  
19 damage which we are seeing with this device and which you  
20 saw in these pictures is order of magnitude greater than  
21 the maximum extent of tubal damage which I see in patients  
22 with ectopic pregnancies. We routinely with an ectopic  
23 pregnancy take a section from the pregnancy to document the  
24 presence of the pregnancy and then for medical and legal  
25 reasons, we always take sections from the non-ectopic

1 portion of the tube in order to document is there  
2 follicular salpingitis? Is there chronic salpingitis, et  
3 cetera, for medical-legal issues?

4 We never see in those cases this degree of  
5 tubal occlusion and this degree of tubal damage that we're  
6 getting with this device. So that's all I can say. I have  
7 never seen a tube which I am sure has become recanalized.  
8 What I can say is that the extent of damage with this  
9 device is much more than what we see in patients with  
10 ectopic pregnancies.

11 DR. SEIFER: And just for the record, do we  
12 have any understanding of how recanalization occurs?

13 DR. WRIGHT: I do not.

14 DR. BLANCO: Any other questions? Anyone from  
15 this side?

16 DR. SHARTS-HOPKO: Could somebody assure me  
17 about your confidence in tissue compatibility with the  
18 steel and the nickel titanium?

19 MS. DOMECUS: I will have our vice president of  
20 research and development, Ashish Khera, address the  
21 biocompatibility testing that's been done. Is that your  
22 question?

23 MR. KHERA: Good morning.

24 DR. BLANCO: I'm sorry. First introduce  
25 yourself, although you did a little bit.

1 MR. KHERA: My name is Ashish Khera. I'm the  
2 vice president of research and development for Conceptus,  
3 Inc.

4 The materials for the Essure Micro-Insert were  
5 chosen for their long history in use in medical  
6 applications. Specifically, nickel titanium alloy has been  
7 used in medical implants for over 30 years. The stainless  
8 steel that's on the device has also been used for over 30  
9 years as medical implant. The testing that was conducted  
10 on the devices was long-term implant testing as required by  
11 FDA and ISO guidelines.

12 DR. BLANCO: Thank you.

13 MS. DOMECUS: If I can add to that, the panel  
14 was not supplied with the summary of biocompatibility  
15 testing that we supplied in the PMA in an effort to make  
16 sure your packages were not unduly long.

17 Anyway, I wanted to let you know that our  
18 biocompatibility test plan was submitted to FDA early on.  
19 We got feedback from the FDA. We've conducted all of the  
20 biocompatibility tests required in the FDA guidelines. The  
21 protocols for the chronic toxin mutagenicity testing were  
22 submitted to the FDA in advance of conducting those tests.  
23 Those results were submitted in the PMA, and it's been  
24 shown that it's not toxic in the chronic setting and it's  
25 not mutagenic as well as other studies in muscle

1     implantation, sensitization, vaginal irritation, et cetera.  
2     The whole battery of tests that's required for this  
3     category of implant were conducted and those results were  
4     submitted in the PMA.

5             DR. BLANCO: Thank you.

6             MS. DOMECUS: Does that answer your question?

7             DR. BLANCO: Subir?

8             DR. ROY: Could I ask Dr. Cooper a few  
9     questions?

10            Inasmuch as hysteroscopy could be construed as  
11    being a clean contaminated procedure, there's some who  
12    would have used prophylactic antibiotics at the time of  
13    performance of this procedure, and I take it that was a  
14    deliberate decision not to be employed?

15            DR. COOPER: It was my understanding that this  
16    was left to the discretion of the investigator and only one  
17    of the investigators in the pivotal trial made routine use  
18    of prophylactic antibiotics.

19            DR. ROY: Okay. Inasmuch as Dr. Wright  
20    described the profound inflammatory response that does  
21    occur with this device, what was done when perforations  
22    were noted?

23            DR. COOPER: When perforations were noted, the  
24    patients were deemed to be candidates for traditional  
25    methods of sterilization. The devices were retrieved at

1 laparoscopy.

2 DR. ROY: With I suppose a bit more surgical  
3 intervention that traditionally would occur or did they  
4 just slip out?

5 DR. COOPER: No, the diagnosis of perforation  
6 was in most cases made at the time of device placement. In  
7 a small number of cases, perforation was not noted until  
8 the three-month post-procedure x-ray. Retrieval of the  
9 device at laparoscopy was not found to be problematic. In  
10 a couple of the cases, the device was found lying in the  
11 omentum but could be easily removed from the omentum.

12 DR. ROY: Okay. Because it's sort of like the  
13 situation with copper IUDs being perforated. They produce  
14 such an inflammatory response, that it is somewhat  
15 problematic, depending on where you ultimately find them,  
16 whether the omentum is able to sequester them or other  
17 peritoneal or intraabdominal contents, such as bowels. So  
18 I was just curious to what extent the inflammatory process,  
19 even at a three-month interval, was sufficiently  
20 problematic, and I guess you're telling me that it was not,  
21 it was easy to find and remove without resorting to  
22 laparotomy, for example, to do so.

23 DR. COOPER: Dr. Carignan can speak to this  
24 perhaps, but I don't recall any of the patients required  
25 laparotomy for device removal.

1 DR. BLANCO: And let me ask you a follow-up on  
2 that. So did I understand you correctly that in the  
3 perforations that you did have, most of them were not  
4 recognized until your follow-up hysterosalpingogram, I  
5 guess, or x-ray for placement three months later, is that  
6 correct?

7 DR. COOPER: Dr. Carignan can speak to this.

8 MS. DOMECUS: The protocol actually didn't ask  
9 for a diagnosis of adverse events that can prevent  
10 reliance, such as perforation, until the three-month time  
11 point because conceivably someone on the day zero x-ray  
12 could have had a device that was well located and then on a  
13 three-month follow-up could have had an expelled device.  
14 So we actually ask in the protocol for them not to take  
15 action based on the day zero x-ray. The perforations were  
16 noted, though, at the three-month follow-up visit as well  
17 as the day zero x-ray and one physician did take action  
18 based on the day zero perforation.

19 Dr. Carignan can address maybe in more detail  
20 the earlier questions about device retrieval in those  
21 perforated patients who went on to subsequent tubal  
22 ligation.

23 DR. BLANCO: Okay. Go ahead.

24 DR. CARIGNAN: So in both the pivotal trial and  
25 Phase II, we had nine women undergo laparoscopic

1 sterilization procedure with five removals prior to their  
2 reliance on the device. In the pivotal trial, there were  
3 four sterilizations performed. Two of them had retrieval  
4 of devices and two did not have retrieval. In the Phase II  
5 study, in the prereliability phase, we also had five women  
6 undergo sterilization procedures. Three of them had  
7 retrieval and two did not.

8 We've had no postreliance women in the pivotal  
9 trial undergo any surgery to remove devices but we have had  
10 two women in the Phase II undergo surgery, both of them  
11 with perforations. One of them underwent just a typical  
12 laparoscopic sterilization with a retrieval and the other  
13 woman did undergo a laparotomy to remove a device. So of  
14 the retrievals that we had of 11, only one underwent  
15 laparotomy, mainly because it was the standard of care of  
16 the doctor that did the removal. Of the women whose  
17 devices have not been retrieved, we've not had any reports  
18 of unusual pain that can be attributed to the device  
19 location.

20 DR. BLANCO: Let me get a follow up. In  
21 perforations, it is typical in a lot of the devices that  
22 other OB/GYNs or at least this OB/GYN is familiar with, the  
23 device is actually moved into placement as opposed to the  
24 way the technique is here where the catheter is moved away.

25 Is there any fail-safe mechanisms in the way

1 your device is handled that someone can make the mistake of  
2 advancing this process further into the tube, rather than  
3 removing the catheter? Do you understand what I'm asking?

4 DR. CARIGNAN: Yes. The fail safe that's built  
5 into the design is related to the black bump at the time of  
6 initial positioning. Then during the training, we stress  
7 maintaining that position during the release of the device.

8 The other thing that we emphasize during  
9 training is if you experience what we define as a sudden  
10 loss of resistance, so that you feel that you're going into  
11 the tube, and suddenly you feel like a little, you know,  
12 pop, that you would then recognize that as a potential  
13 perforation and not place the device and that's part of the  
14 training program that we emphasize.

15 DR. BROWN: Specific to the patients, the nine  
16 patients you just talked about, were all of those patients  
17 that had the current iteration of the device, because I  
18 thought there was something mentioned about a patient who  
19 had to have cornual resections and that was with a previous  
20 iteration of the device?

21 DR. CARIGNAN: The one that had the cornual  
22 resection was one of our early Phase II patients and after  
23 two years of reliance began having some pain with menses  
24 and she requested to have the device removed. So she was  
25 one of our earlier patients from early 199.

1 DR. BROWN: But was that --

2 DR. CARIGNAN: The current design.

3 DR. BROWN: That was with the current design?

4 DR. CARIGNAN: Correct.

5 DR. BROWN: Why was cornual resection necessary  
6 in that case?

7 DR. CARIGNAN: Because the device spans the  
8 utero-tubal junction, the way to get it out is to do a  
9 cornual resection.

10 DR. BLANCO: A follow-up on that, because I had  
11 that as a question. On the patients that had continual --  
12 you said a few questions, I forgot the exact number, had  
13 continual symptomatology of cramps and pains and so forth.  
14 What other experience except other than this one case do  
15 you have for someone who has chronic complaint, desires the  
16 removal of the device, in terms of removing the device? Is  
17 cornual section the only option for removal of the device  
18 if someone wants it removed? Do you see what I'm saying?

19 In other words, can you go back, do you have  
20 any experience going back with hysteroscope trying to pull  
21 the device out or do you have to resect the corneum?

22 DR. CARIGNAN: When a device is well positioned  
23 across the utero-tubal junction, because of the extensive  
24 fibrosis, it does require a minimal cornual resection to  
25 remove the device. The only time that we ever actually

1 recommend removal of the device hysteroscopically is if  
2 during the procedure, you recognize that you haven't  
3 positioned it far enough into the tube or you inadvertently  
4 deploy it into the uterus that you would then remove it and  
5 replace the device. Subsequent to placement, we do not  
6 recommend hysteroscopic removal of a well-positioned  
7 device.

8 DR. NOLLER: Question.

9 DR. BLANCO: Go ahead.

10 DR. NOLLER: I have a question regarding the  
11 training plan. It wasn't clear to me. In the five cases  
12 that are precepted, is there a requirement that those all  
13 be done under local anesthesia?

14 MS. DOMECUS: Anesthesia is always left up to  
15 the choice of the physician. There's no requirement that  
16 it be done under local.

17 DR. NOLLER: Even during the training?

18 MS. DOMECUS: Correct.

19 DR. NOLLER: Thank you.

20 DR. SHIRK: I had some questions for Dr.  
21 Cooper.

22 There's not any discussion about preexisting  
23 pathology found at the time of hysteroscopy. As any of us  
24 who do hysteroscopy know that we do find occasionally, you  
25 know, pathology in the uterine cavity, and I would assume

1     that's not previously been diagnosed. How many of these  
2     patients had preexisting pathology in the uterine cavity,  
3     and how would you recommend that this be handled?

4             DR. COOPER: First of all, you may recall that  
5     years ago, I had considerable experience with another  
6     hysteroscopic sterilization technique and as part of that  
7     experience, I studied what was the rate of intercavitary  
8     pathology found at the time of an elective sterilization  
9     procedure and was amazed to find that in fact it was a very  
10    low incidence of pathology and rarely did the pathology  
11    interfere with the ability to identify and place the  
12    device.

13            In this case, as Dr. Carignan showed you, I  
14    think there were 11 cases of women undergoing hysteroscopy  
15    in whom devices could not be placed because the tubal ostia  
16    could not be identified and that would include women who  
17    had cornual pathology, such as fibroids or polyps, that  
18    would obscure the view of the tubal ostia or perhaps  
19    intrauterine adhesions that had scarred the fallopian tube  
20    making them not visible. But as a general rule, the young  
21    woman with no abnormal menstrual complaints is unlikely to  
22    have intracavitary pathology which would preclude the  
23    ability to place the devices.

24            DR. SHIRK: If you, say, found a small  
25    submucosal fibroid, would you continue to place the device?

1 DR. COOPER: I would.

2 DR. BLANCO: Dr. Brown?

3 DR. BROWN: In the Volume 1 of what we  
4 received, there was a statement made, and I think it's  
5 also, I believe, on the labeling information that there is  
6 limited to no information about subsequent surgical  
7 procedures, including D&Cs, endometrial biopsies,  
8 hysterectomies, in these patients, and my question was in  
9 the follow-up, have you actually had patients who've had  
10 devices placed that have had to have, say, a D&C for  
11 abnormal bleeding, and do you recommend that those patients  
12 are -- I interpret it was implied that at that point. They  
13 can no longer reliably rely on this method of contraception  
14 or what do you tell somebody, say, who needs a D&C for  
15 abnormal bleeding, who has had this device in for two  
16 years? Does she need to use something else?

17 DR. COOPER: Thank you for I think an important  
18 question.

19 We have experience in two of the four women who  
20 had luteal phase pregnancies, chose pregnancy termination.  
21 The procedure was accomplished with a suction D&C. Despite  
22 the fact that the devices had not been worn for the  
23 requisite three-month period of time, in neither case were  
24 the devices disrupted with the suction D&C, and women went  
25 on to rely on the Essure devices for long-term

1     contraception.

2             We also have in the commercial population  
3     reports of five women who have undergone D&C for evaluation  
4     of abnormal bleeding with no disruption of the device, and  
5     it has been my experience as a clinician for many years  
6     that the routine evaluation of the woman with abnormal  
7     bleeding generally consists of a papule endometrial biopsy.  
8     Even a vigorous and thorough papule endometrial biopsy  
9     probably samples less than four percent of the endometrial  
10    surface. I find it all but impossible to imagine that the  
11    suction that is created with a papule catheter could  
12    dislodge or interrupt a properly placed Essure device,  
13    particularly given its three-month period of time to allow  
14    for tissue ingrowth.

15            DR. BROWN: So what do you tell the patients?  
16    So what would the labeling specifically say about patients  
17    who have to have these procedures subsequently?

18            DR. COOPER: I would suggest that women who  
19    experience abnormal uterine bleeding who are wearing this  
20    device or, for that matter, any woman experiencing abnormal  
21    bleeding undergo a visual evaluation of the uterine cavity,  
22    to include diagnostic hysteroscopy, and I think that makes  
23    good sense, whether a woman is an Essure device-wearer or  
24    not.

25            DR. BROWN: Okay. And then, can you comment

1 about also the mention that electrocautery should not be  
2 used in women who are having, I would imagine,  
3 hysterectomies or other procedures? Is that because of a  
4 risk of burning or sparking or what? Could you comment  
5 from the biophysical -- I mean, how would that happen  
6 exactly?

7 DR. COOPER: Again, the recommendation or the  
8 labeling suggests that we would -- we don't have enough  
9 information at this point in time, given the length of the  
10 trial, to speak to this, but we have admonished or warned  
11 physicians to not use electrocautery within a four-  
12 centimeter length from the Essure device, and we do know  
13 that at hysteroscopic endometrial ablation used with  
14 rollerball, again in the commercial population, not in the  
15 clinical trial, we know that procedures have been done and  
16 have been done safely which would suggest that the  
17 physician has visual control of the rollerball electrode  
18 and is keeping the electrode a safe distance from the  
19 device.

20 DR. BROWN: What would happen if you touched  
21 the electrode to the coils that are sticking into the -- I  
22 mean, what would physically happen?

23 DR. COOPER: Let me have Dr. Carignan speak to  
24 that.

25 DR. CARIGNAN: As we showed you earlier, we had

1 quite extensive pre hysterectomy and perihysterectomy  
2 studies that were conducted with the devices in situ.  
3 During those procedures, electrocautery was used very  
4 commonly. We did recommend that they stay clear of the  
5 device for the reasons that Dr. Cooper has outlined. In  
6 one instance where the device was touched where that ball  
7 would basically be going through, you could see that there  
8 was a little blanching of the tube. So we do recognize  
9 that with our RF-type energies, it is likely to conduct  
10 when it's touched.

11 DR. BLANCO: All right. Let's go ahead and  
12 start wrapping it up because it's getting time for the  
13 break. So if we have a couple of other questions of fact.

14 DR. O'SULLIVAN: I still am having a little bit  
15 of trouble understanding how this device creates adhesions  
16 in the fallopian tube, yet when the device is in the  
17 peritoneal cavity, that doesn't seem to happen. Is that  
18 what I'm understanding, and if so, why not?

19 MS. DOMECUS: I'll ask Dr. Wright to come to  
20 the podium again since he did the histological analysis of  
21 the devices in both of those categories.

22 DR. WRIGHT: In the tube, probably one of the  
23 initial inciting events is the fact that you have this  
24 outer coil which expands out and causes, I assume, trauma  
25 to the epithelium and to the plicae extending in from the

1 tube wall, into the lumen, and that sort of trauma then  
2 probably starts stimulating the entire inflammatory  
3 response which then generates the fibrotic response.

4 In the two tubes which we have looked at  
5 histopathologically, the two devices which we process which  
6 were retrieved from the peritoneal cavity, both of those  
7 showed some inflammatory infiltrate and some fibrosis  
8 immediately around the inner coil which is where the PET  
9 fibers are. So you're going to have macrophages and  
10 inflammatory cells free in the peritoneal cavity. They are  
11 going to sit there. You're going to get some fibrosis.

12 What we did not see with those from the  
13 sections of them was dense adhesions and dense fibrosis of  
14 bowel or anything or adipose tissue tightly adherent to the  
15 Micro-Inserts. Why we're seeing the difference there, yet  
16 compared to what you're seeing in the tube, I'm not sure,  
17 unless it's due to the fact that when it's in place in the  
18 tube, you've caused damage with the outer coil generating  
19 this whole cascade of events.

20 DR. O'SULLIVAN: One last question. What was  
21 the longest period of time one of these was retrieved from  
22 the time of perforation to the time it was retrieved? What  
23 was the longest period of time?

24 DR. WRIGHT: I'd have to ask Chuck because I  
25 was blinded to all the wearing times and we only unblinded

1 me to the tubes recently. Chuck, what were the times, the  
2 longest time?

3 DR. CARIGNAN: The longest time that we have  
4 with any iteration that used the PET fibers in a similar  
5 configuration was actually a patient with the beta design  
6 who just recently had her devices removed after just about  
7 four years of them being in place, and one of the devices  
8 was in the pouch of Douglas and when the surgeon went in,  
9 he was able to just laparoscopically go in, identify the  
10 device and pull it right out.

11 DR. O'SULLIVAN: Do you know why? I mean,  
12 you're still assuming, Dr. Wright, that this is all related  
13 to the fact that it's trauma initially?

14 DR. WRIGHT: I think it's very different when  
15 you have a device with PET fibers sitting in a "closed  
16 cavity" than when you have that same sort of device free in  
17 the peritoneum.

18 DR. BLANCO: Let me go ahead because we're  
19 starting to run a little late on time, cut it short. You  
20 might just want to consider in some of your  
21 biocompatibility data, you probably did some studies of  
22 putting the device inside animal models and looking for  
23 adhesions. So maybe you can look that up and see if you  
24 can bring forth any information that might try to answer  
25 that issue on that, and then I think we have one question